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(54) Title: USE OF DIFFERENTIALLY EXPRESSED NUCLEIC ACID SEQUENCES AS BIOMARKERS FOR CANCER

(57) Abstract: The present invention relates to novel marker sequences that are differentially expressed in cancer cells or tissue of a subject with cancerous conditions. The present invention also relates to assays for diagnosis, prognosis, staging, monitoring, therapeutic treatment, and marker sequence related agents including probes, primers, antibodies, and therapeutic compositions.

WO 2005/044990 A2

**USE OF DIFFERENTIALLY EXPRESSED NUCLEIC ACID SEQUENCES AS  
BIOMARKERS FOR CANCER**

**Field of the Invention**

The present invention relates to methods for diagnosis, prognosis, characterization,  
5 management, and therapy of cancer including colon cancer, based on the identification of certain  
colon cancer-associated differentially expressed marker sequences.

**Background of the Invention**

Cancers are the second leading cause of death, next to cardiovascular disease, in the  
United States. The pathological and molecular mechanisms for cancer initiation and promotion  
10 have been revealed after decades of researches. Many genes are involved in the initiation and  
progression of cancers, including oncogenic and tumor suppressive genes. Multiple factors  
including genetic, endocrinologic, immunologic, and environmental factors, intertwine in the  
process of transformation and progression of cancers. The control and cure of cancers remain to  
be one of the most challenging health care tasks. Particularly, one of the most pressing health  
15 issues today is diagnosing, monitoring, and treating cancer.

Colorectal carcinoma is a malignant neoplastic disease. There is a high incidence of  
colorectal carcinoma in the Western world, particularly in the United States. Tumors of this type  
often metastasize through lymphatic and vascular channels. Many patients with colorectal  
carcinoma eventually die from this disease. In fact, it is estimated that 62,000 persons in the  
20 United States alone die of colorectal carcinoma annually.

However, if diagnosed early, colon cancer may be treated effectively by surgical removal  
of the cancerous tissue. Colorectal cancers originate in the colorectal epithelium and typically  
are not extensively vascularized (and therefore not invasive) during the early stages of  
development. Colorectal cancer is thought to result from the clonal expansion of a single mutant  
25 cell in the epithelial lining of the colon or rectum. The transition to a highly vascularized,  
invasive and ultimately metastatic cancer which spreads throughout the body commonly takes  
ten years or longer. If the cancer is detected prior to invasion, surgical removal of the cancerous  
tissue is an effective cure. However, colorectal cancer is often detected only upon manifestation  
of clinical symptoms, such as pain and black tarry stool. Generally, such symptoms are present  
30 only when the disease is well established, often after metastasis has occurred, and the prognosis

for the patient is poor, even after surgical resection of the cancerous tissue. Early detection of colorectal cancer therefore is important in that detection may significantly reduce its morbidity.

Invasive diagnostic methods such as endoscopic examination allow for direct visual identification, removal, and biopsy of potentially cancerous growths such as polyps. Endoscopy is expensive, uncomfortable, inherently risky, and therefore not a practical tool for screening populations to identify those with colorectal cancer. Non-invasive analysis of stool samples for characteristics indicative of the presence of colorectal cancer or precancer is a preferred alternative for early diagnosis, but no known diagnostic methods are available which reliably achieve this goal.

### Summary of the Invention

The present invention relates to nucleic acid sequences that are differentially expressed in cancer tissue compared to normal tissue, and various methods, reagents and kits for diagnosis, staging, prognosis, monitoring and treatment of cancer, including colon cancer.

In one aspect, the present invention provides methods for determining the expression levels of individual and/or combinations of the differentially expressed marker sequences in a biological sample that are indicative of the presence, or stage of the disease, or the efficacy of therapy. The method comprises contacting said sample with a polynucleotide probe or a polypeptide ligand under conditions effective for said probe or ligand to hybridize specifically to a nucleic acid or a polypeptide in said sample, and detecting the presence or absence of marker sequences. In one embodiment, methods are provided to determine the amounts and/or the differentially expressed levels at which the marker sequences of the present invention are expressed in samples. Such methods can comprise contacting said sample with a polynucleotide probe or a polypeptide ligand under conditions effective for said probe to hybridize specifically to the nucleic acids in said sample, and detecting the amounts or differentially expressed level of the marker sequences. In one preferred embodiment, said polynucleotide probe is a polynucleotide designed to identify one of the marker sequences in Tables 1 and 2. In another preferred embodiment, said polypeptide ligand is an antibody.

In another aspect, the present invention provides probes and primers designed to detect transcripts or genomic sequences corresponding to one or more marker sequences of the present

invention. The probes and primers may comprise a portion or all of the sequences listed in SEQ ID NOs: 1-93, or sequences complementary thereto, or sequences which hybridize under stringent conditions to a portion or all of SEQ ID NOs: 1-93.

5 In another aspect, the present invention provides polypeptides encoded by the marker sequences, biologically active portions thereof, and polypeptide fragments suitable for use as immunogens to raise antibodies directed against polypeptides of the marker sequences of the present invention.

10 In another aspect, the present invention provides ligands directed to polypeptides and fragments thereof of the marker sequences of the present invention. Preferably, said polypeptide ligands are antibodies. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, or chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic antibodies, or other epitope binding polypeptide. Preferably, an antibody, useful  
15 in the present invention for the detection of the individual marker sequences (and optionally at least one additional colon cancer-specific marker), is a human antibody or fragment thereof, including scFv, Fab, Fab', F(ab'), Fd, single chain antibody, or Fv. Antibodies, useful in the invention may include a complete heavy or light chain constant region, or a portion thereof, or an absence thereof.

20 Another aspect of the present invention provides a method of assessing whether a subject is suffering from or at risk of developing cancer including colon cancer by detecting the differential expression of the marker sequences of the present invention. In one embodiment, the diagnostic method comprises determining whether a subject has an abnormal mRNA or cDNA and/or protein level of the marker sequences. The method comprises detecting the expression level of the individual and/or the combinations of the marker sequences in a biological sample  
25 obtained from a patient. Specifically, the method comprises:

(1). Providing a nucleic acid probe comprising a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a



portion of the coding sequence of a nucleic acid sequence represented by SEQ ID NOs:1-93, or a sequence complementary thereto;

(2). Obtaining a clinical sample from a patient potentially comprising one or more nucleic acid marker sequences;

5 (3). Providing a second clinical sample from an individual known to not have colon cancer, or a cancer-free tissue of the same patient;

(4). Contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second clinical samples (e.g., in a Northern blot or in situ hybridization assay); and

10 (5). Comparing (a) the amount of hybridization of the probe with RNA of the first serum sample, with (b) the amount of hybridization of the probe with RNA of the second clinical sample; wherein a statistically change (e.g., either an increase or a decrease) in the amount of hybridization with the RNA of the first clinical sample as compared to the amount of hybridization with the RNA of the second clinical sample is indicative of the presence of one or more marker sequences in the first clinical sample.

15 In another embodiment, the diagnostic methods comprise detecting the polypeptides encoded by the marker sequences of the present invention. The assay would include contacting the polypeptides of the test cell or tissue with one or more polypeptide ligands specific for the polypeptides represented by SEQ ID NOs: 94-186, and determining the approximate amount of complex formation by the ligands and polypeptides of the test cell or tissue, wherein a  
20 statistically significant difference (either an increase or a decrease) in the amount of the complex formed with the polypeptides of a test cell or tissue as compared to a normal cell or tissue is an indication that the test cell is cancerous or pre-cancerous. In particular, the assay evaluates the level of marker polypeptide in the test cells, and preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell and/or a transformed  
25 cell of known phenotype.

In another aspect, the present invention provides DNA and protein microarrays for detecting the differential expression levels of the marker sequences. In some embodiments, the microarrays comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, or more nucleic acids that are complimentary to at least a portion of the coding sequences of the marker sequences

represented by SEQ ID NOs: 1-93. In some embodiments, the microarrays comprise antibodies or antigen-binding fragments thereof, that specifically bind to at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 different marker polypeptides encoded by nucleic acids comprising a nucleotide  
5 sequence selected from the group consisting of SEQ ID NOs: 1-93. In one embodiment, the probe/primer can comprise a sequence that hybridizes under stringent conditions to at least about 7, preferably 12, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400, or more consecutive nucleotides of SEQ ID NOs: 1-93 of the present invention. In another embodiment, the probe/primer can comprise a sequence that hybridizes  
10 under moderately stringent conditions to at least about 7, preferably 12, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400, or more consecutive nucleotides of SEQ ID NOs: 1-93 of the present invention.

In another aspect, the present invention provides methods for determining cancer prognosis and stage based on examining the expression levels of the nucleic acid marker  
15 sequences and polypeptides using the methods described in the present invention.

In one embodiment, the methods comprise:

(1). detecting in a biological sample of the subject at a first point in time, the expression of one or more nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93;

20 (2). repeating step (a) at a subsequent point in time; and

(3). comparing the expression level detected in steps (a) and (b), wherein a change in the expression level is indicative of progression of cancer or a pre-malignant condition thereof in the subject.

In another embodiment, the methods comprise:

25 (1). detecting in a biological sample of the subject at a first point in time, the expression of one or more polypeptides comprising one or more polypeptide sequences selected from the group consisting of SEQ ID NOs: 94-186;

(2). repeating step (a) at a subsequent point in time; and

(3). comparing the expression level detected in steps (a) and (b), wherein a change in the expression level is indicative of progression of cancer or a pre-malignant condition thereof in the subject.

In another aspect, the present invention also provides methods that permit the assessment and/or monitoring of patients who will be likely to benefit from both traditional and non-traditional treatments and therapies for cancers, particularly colon cancer. The methods include assessing the levels of one or more of the marker sequences in a biological sample for the purposes of determining the status of a patient's disease an/or the efficacy, reaction, and response to cancer or neoplastic disease treatments or therapies that the patient is undergoing.

The present invention also includes methods of assessing the efficacy of a test composition for inhibiting cancer including colon cancer. The methods comprise comparing expression levels of one or more marker sequences in a first biological sample maintained in the presence of a test composition with the expression levels of the same marker sequences in a second biological sample maintained in the absence of the test composition.

In another aspect, the present invention provides assays for determining compounds that modulate the biological activity of the nucleic acids or the polypeptides encoded by the marker sequences. Methods of identifying compounds generally comprise steps in which a compound is placed in contact with a marker sequence, its transcription product, its translation product, or other target, and determination of whether the compound modulates the marker sequence.

In another aspect, the present invention also provides methods for screening drugs that inhibit cancer including colon cancer. Drug screening is performed by adding a test compound to a sample of cells and monitoring the effect. The screening methods may include both *in vitro* and *in vivo* screening of a cell or tissue.

In another aspect, the present invention also provides kits for determining the differential expression levels of the marker sequences of the present invention in a biological sample. Such kits can be used to determine (1) presence or absence of cancer, (2) prognosis and stage of cancer, (3) drugs that inhibit cancer, and (4) treatment for cancer.

## Detailed Description of the Invention

### I General

The present invention is based, in part, on the identification of marker sequences that are differentially expressed (including both over- and under-expression of the sequences) in various types of humans cells (i.e., cells obtained from a human, cultured human cells, archived or preserved human cells, and *in vivo* cells) relative to normal (i.e., non-cancerous) human cells. It has been discovered that the level of expression of individual marker sequences and combinations of marker sequences described in the present invention correlates with the presence of cancer or pre-malignant condition in a patient. The expression of one or more marker sequences in human cells can be assessed by detecting the RNA transcripts and/or proteins encoded by the marker sequences. Accordingly, the present invention provides methods for identifying cancer, particularly colon cancer, in an individual by screening for sequences which are over- or under-expressed in cancerous cells relative to the level of expression in normal cells, such as cells from colon tissue. Particularly, the present invention provides a method for the identifying colon cancer in an individual by detecting individual marker sequences and/or combinations of marker sequences in the individual relative to a control expression level of the marker sequences in an individual without cancer. The present invention further provides methods for monitoring the onset, progression, or regression of cancer, particularly colon cancer, in an individual by monitoring the expression level of individual marker sequences and/or combinations of marker sequences in the individual at different points in time. The present invention further provides methods for assessing the efficacy of a therapy for inhibiting cancer, particularly colon cancer in a patient by comparing the expression level of individual marker sequences and/or combinations of marker sequences in the individual prior to and after the therapeutic treatment. The present invention further provides methods for selecting a composition for inhibiting cancer, particularly colon cancer, in a patient by comparing the expression level of individual marker sequences and/or combinations of marker sequences in the presence and absence of the composition. The present invention further provides methods for inhibiting cancer, particularly colon cancer, in a patient by administering to the patient a therapeutic composition, wherein the efficacy of the therapeutic composition is indicated by the change in the expression level of individual marker sequences and/or combinations of marker sequences.

In addition to the above methods, the present invention also provides compositions and various kits for the use in the above methods.

## II Definitions

As used herein, the term "differentially expressed" refers to expression levels in a test  
5 cell that differ significantly from levels in a reference cell, e.g., mRNA is found at levels at least about 25%, at least about 50% to about 75%, at least about 90% increased or decreased, generally at least about 1.2-fold, at least about 1.5-fold, at least about 2-fold, at least about 5-fold, at least about 10-fold, or at least about 50-fold or more increased or decreased in a cancerous cell when compared with a cell of the same type that is not cancerous. The  
10 comparison can be made between two tissues, for example, if one is using in situ hybridization or another assay method that allows some degree of discrimination among cell types in the tissue. The comparison may also be made between cells removed from their tissue source. "Differential expression" refers to both quantitative, as well as qualitative, differences in the genes' temporal and/or cellular expression patterns among, for example, normal and neoplastic tumor cells,  
15 and/or among tumor cells which have undergone different tumor progression events.

As used herein, the term "a biological sample" refers to a whole organism or a subset of its tissues, cells or component parts (e.g. body fluids, including but not limited to blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid and semen). "A biological sample" further refers to a homogenate, lysate or  
20 extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, organs. Most often, the sample has been removed from an animal, but the term "biological sample" can also refer to cells or tissue analyzed *in vivo*, i.e.,  
25 without removal from animal. Typically, a "biological sample" will contain cells from the animal, but the term can also refer to non-cellular biological material, such as non-cellular fractions of blood, saliva, or urine, that can be used to measure the cancer-associated polynucleotide or polypeptides levels. "A biological sample" further refers to a medium, such as a nutrient broth or gel in which an organism has been propagated, which contains cellular  
30 components, such as proteins or nucleic acid molecules.

As used herein, the term "nucleic acid" refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. ESTs, chromosomes, cDNAs, mRNAs, and rRNAs are representative examples of molecules that may be referred to as nucleic acids.

As used herein, the term "change in the expression level" refers to either an increase or a decrease of the expression level in a test sample from the control level by an amount greater than the standard error of the assay employed to assess expression. Preferably, the change is by at least about twice, and more preferably three, four, five or ten times that amount. For increase, the change is determined by comparing the expression level in the test sample to the control level. For decrease, the change is determined by comparing the control level to the expression level in the test sample. Alternatively, the decrease is determined by comparing the expression level in the test sample to the control level and the decrease in the expression level is by at least about 15%, 25%, 30%, 40%, 50%, 65%, 80%, or greater. The term "significant change in the specific binding" refers to either an increase or a decrease from the specific binding in the cancer-free sample by at least about 10%, 20%, 25%, 30%, preferably at least about 40%, 50%, more preferably at least about 60%, 70%, or 90%.

As used herein, the term "expression level of one or more nucleic acid sequences" refers to the amount of mRNA transcribed from the corresponding genes that are present in a biological sample. The expression level can be detected with or without comparison to a level from a control sample or a level expected of a control sample.

As used herein, the term "control expression level of one or more nucleic acid sequences" refers to the amount of mRNA transcribed from the corresponding genes that are present in a biological sample representative of healthy, cancer-free subjects. The term "control expression level" can also refer to an established level of mRNA representative of the cancer-free population, that has been previously established based on measurement from healthy, cancer-free subjects.

As used herein, the term "cancerous cell" or "cancer cell", used either in the singular or plural form, refers to cells that have undergone a malignant transformation that makes them

pathological to the host organism. Malignant transformation is a single- or multi-step process, which involves in part an alteration in the genetic makeup of the cell and/or the gene expression profile. Malignant transformation may occur either spontaneously, or via an event or combination of events such as drug or chemical treatment, radiation, fusion with other cells, viral infection, or activation or inactivation of particular genes. Malignant transformation may occur in vivo or in vitro, and can if necessary be experimentally induced. Malignant cells may be found within the well-defined tumor mass or may have metastasized to other physical locations. A feature of cancer cells is the tendency to grow in a manner that is uncontrollable by the host, but the pathology associated with a particular cancer cell may take any form. Primary cancer cells (that is, cells obtained from near the site of malignant transformation) can be readily distinguished from non-cancerous cells by well-established pathology techniques, particularly histological examination. The definition of a cancer cell, as used herein, includes not only a primary cancer cell, but any cell derived from a cancer cell ancestor. This includes metastasized cancer cells, and in vitro cultures and cell lines derived from cancer cells.

As used herein, the term "efficacy" refers to either inhibition to some extent, of cell growth causing or contributing to a cell proliferative disorder, or the inhibition, to some extent, of the production of factors (e.g., growth factors) causing or contributing to a cell proliferative disorder. "A therapeutic efficacy" refers to relief of one or more of the symptoms of a cell proliferative disorder. In reference to the treatment of a cancer, a therapeutic efficacy refers to one or more of the following: 1) reduction in the number of cancer cells; 2) reduction in tumor size; 3) inhibition (i.e., slowing to some extent, preferably stopping) of cancer cell infiltration into peripheral organs; 3) inhibition (i.e., slowing to some extent, preferably stopping) of tumor metastasis; 4) inhibition, to some extent, of tumor growth; and/or 5) relieving to some extent one or more of the symptoms associated with the disorder. In reference to the treatment of a cell proliferative disorder other than a cancer, a therapeutic efficacy refers to 1) either inhibition to some extent, of the growth of cells causing the disorder; 2) the inhibition, to some extent, of the production of factors (e.g., growth factors) causing the disorder; and/or 3) relieving to some extent one or more of the symptoms associated with the disorder.

As used herein, the term "detectable label" refers to a composition detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means.

As used herein, the term "a polynucleotide probe" refers to a nucleic acid capable of binding to a target nucleic acid of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation. As used herein, a probe may include natural (i.e., A, G, C, or T) or modified on bases (7-deazaguanosine, inosine, etc.) or on sugar moiety. In addition, the bases in a probe may be joined by a linkage other than a phosphodiester bond, so long as it does not interfere with hybridization. Thus, for example, probes may be peptide nucleic acids in which the constituent bases are joined by peptide bonds rather than phosphodiester linkages. It will be understood by one of skill in the art that probes may bind target sequences lacking complete complementarity with the probe sequence depending upon the stringency of the hybridization conditions. The probes are preferably directly labeled as with isotopes, chromophores, lumiphores, chromogens, or indirectly labeled such as with biotin to which a streptavidin complex may later bind. By assaying for the presence or absence of the probe, one can detect the presence or absence of the select sequence or subsequence.

As used herein, the term "hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

As used herein, the term "subject" refers to any human or non-human organism.

As used herein, "individual" refers to a mammal, preferably a human.

As used herein, "detecting" refers to the identification of the presence or absence of a molecule in a sample. Where the molecule to be detected is a polypeptide, the step of detecting can be performed by binding the polypeptide with an antibody that is detectably labeled. A detectable label is a molecule which is capable of generating, either independently, or in response to a stimulus, an observable signal. A detectable label can be, but is not limited to a fluorescent label, a chromogenic label, a luminescent label, or a radioactive label. Methods for "detecting" a label include quantitative and qualitative methods adapted for standard or confocal microscopy, FACS analysis, and those adapted for high throughput methods involving multi-well plates, arrays or microarrays. One of skill in the art can select appropriate filter sets and excitation energy sources for the detection of fluorescent emission from a given fluorescent polypeptide or dye. "Detecting" as used herein can also include the use of multiple antibodies to a polypeptide to be detected, wherein the multiple antibodies bind to different epitopes on the



polypeptide to be detected. Antibodies used in this manner can employ two or more detectable labels, and can include, for example a FRET pair. A polypeptide molecule is "detected" according to the present invention when the level of detectable signal is at all greater than the background level of the detectable label, or where the level of measured nucleic acid is at all greater than the level measured in a control sample.

As used herein, "detecting" also refers to detecting the presence of a target nucleic acid molecule (e.g., a nucleic acid molecule encoding the marker sequence) refers to a process wherein the signal generated by a directly or indirectly labeled probe nucleic acid molecule (capable of hybridizing to a target, e.g., a sequence encoding Reg1 $\alpha$ , in a serum sample) is measured or observed. Thus, detection of the probe nucleic acid is directly indicative of the presence, and thus the detection, of a target nucleic acid, such as a sequence encoding a marker sequence. For example, if the detectable label is a fluorescent label, the target nucleic acid is "detected" by observing or measuring the light emitted by the fluorescent label on the probe nucleic acid when it is excited by the appropriate wavelength, or if the detectable label is a fluorescence/quencher pair, the target nucleic acid is "detected" by observing or measuring the light emitted upon association or dissociation of the fluorescence/quencher pair present on the probe nucleic acid, wherein detection of the probe nucleic acid indicates detection of the target nucleic acid. If the detectable label is a radioactive label, the target nucleic acid, following hybridization with a radioactively labeled probe is "detected" by, for example, autoradiography. Methods and techniques for "detecting" fluorescent, radioactive, and other chemical labels may be found in Ausubel et al. (1995, *Short Protocols in Molecular Biology*, 3<sup>rd</sup> Ed. John Wiley and Sons, Inc.). Alternatively, a nucleic acid may be "indirectly detected" wherein a moiety is attached to a probe nucleic acid which will hybridize with the target, such as an enzyme activity, allowing detection in the presence of an appropriate substrate, or a specific antigen or other marker allowing detection by addition of an antibody or other specific indicator. Alternatively, a target nucleic acid molecule can be detected by amplifying a nucleic acid sample prepared from a patient clinical sample, using oligonucleotide primers which are specifically designed to hybridize with a portion of the target nucleic acid sequence. Quantitative amplification methods, such as, but not limited to TaqMan, may also be used to "detect" a target nucleic acid according to the invention. A nucleic acid molecule is "detected" as used herein where the level of nucleic acid measured (such as by quantitative PCR), or the level of detectable signal provided by the detectable label is at all above the background level.

As used herein, "detecting" refers further to the early detection of colorectal cancer in a patient, wherein "early" detection refers to the detection of colorectal cancer at Dukes stage A or preferably, prior to a time when the colorectal cancer is morphologically able to be classified in a particular Dukes stage. "Detecting" as used herein further refers to the detection of colorectal cancer recurrence in an individual, using the same detection criteria as indicated above.

"Detecting" as used herein still further refers to the measuring of a change in the degree of colorectal cancer before and/or after treatment with a therapeutic compound. In this case, a change in the degree of colorectal cancer in response to a therapeutic compound refers to an increase or decrease in the expression of the marker sequences including one or more colorectal cancer associated markers, or alternatively, in the amount of the marker polypeptide including one or more colorectal cancer associated markers presented in a clinical sample by at least 10% in response to the presence of a therapeutic compound relative to the expression level in the absence of the therapeutic compound.

As used herein, the term "polypeptide" refers to a polymer in which the monomers are amino acids and are joined together through peptide or disulfide bonds. It also refers to either a full-length naturally-occurring amino acid sequence or a fragment thereof between about 8 and about 500 amino acids in length. Additionally, unnatural amino acids, for example,  $\beta$ -alanine, phenyl glycine and homoarginine may be included. Commonly-encountered amino acids which are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. The L-isomers are preferred.

As used herein, the term "ligand" refers to any compound that interacts with the ligand binding domain of a receptor and modulate its activity. The term "ligand" also refers to a molecule, such as a peptide or variable segment sequence, that is recognized by a particular receptor. As one of ordinary skill in the art will recognize, a molecule (or macromolecular complex) can be both a receptor and a ligand. In general, the binding partner having a smaller molecular weight is referred to as the ligand and the binding partner having a greater molecular weight is referred to as a receptor. Representative ligands include but are not limited to drugs, drug derivatives, isomers thereof, hormones, polypeptides, nucleotides, and the like.

The term "antibody" refers to the conventional immunoglobulin molecule, as well as fragments thereof which are also specifically reactive with one of the subject polypeptides. Antibodies can be fragmented using conventional techniques and the fragments screened for

utility in the same manner as described herein below for whole antibodies. For example, F(ab)<sub>2</sub> fragments can be generated by treating antibody with pepsin. The resulting F(ab)<sub>2</sub> fragment can be treated to reduce disulfide bridges to produce Fab fragments. The antibody of the present invention is further intended to include bispecific, single-chain, and chimeric and humanized molecules having affinity for a polypeptide conferred by at least one CDR region of the antibody. In preferred embodiments, the antibodies, the antibody further comprises a label attached thereto and able to be detected, (e.g., the label can be a radioisotope, fluorescent compound, chemiluminescent compound, enzyme, or enzyme co-factor).

The term "monoclonal antibody" refers to an antibody that recognizes only one type of antigen. This type of antibodies is produced by the daughter cells of a single antibody-producing hybridoma.

As used herein, the terms specific "binding" or "specifically binding", refers to the interaction of an antibody and a protein or peptide. The interaction is dependent upon the presence of a particular structure (*i.e.*, the antigenic determinant or epitope) on the protein; in other words, the antibody is recognizing and binding to a specific protein structure rather than to proteins in general. For example, if an antibody is specific for epitope A, the presence of a protein containing epitope A (or free, unlabeled A) in a reaction containing labeled "A" and the antibody will reduce the amount of labeled A bound to the antibody.

### III Identification of marker sequences

One aspect of the present invention pertains to identification of differentially expressed marker sequences (either over- or under-expressed) in a biological sample from a patient with cancerous or pre-malignant conditions. In general, the method of identifying the marker sequences involves providing a pool of target nucleic acids (derived from both tumor and normal cells and/or tissue) comprising RNA transcripts of one or more target genes, or nucleic acids derived from the RNA transcripts, hybridizing the nucleic acid sample to one or more probes, and detecting the hybridized nucleic acids and calculating a relative expression level relative to the control expression level of the same nucleic acids. A variety of methods have been employed to achieve this end. They include differential screening of cDNA libraries with selective probes, subtractive hybridization utilizing DNA/DNA hybrids or DNA/RNA hybrids, RNA fingerprinting and differential display (Mather, et al. (1981) *Cell* 23:369-378; Hedrick et al.

(1984) *Nature* 308:149-153; Davis et al. (1992) *Cell* 51:987-1000; Welsh et al. (1992) *Nucleic Acids Res.* 20:4965-4970; and Liang and Pardee (1992) *Science* 257:967-971). Recently, PCR-coupled subtractive processes have also been reported (Straus and Ausubel (1990) *Proc. Natl. Sci. USA* 87:1889-1893; Sive and John (1988) *Nucleic Acids Res.* 16:10937; Wieland et al. 5 (1990) *Proc. Natl. Acad. Sci. USA* 87:2720-2724; Wang and Brown (1991) *Proc. Natl. Acad. Sci. USA* 88:11505-11509; Lisitsyn et al. (1993) *Science* 259:946-951; Zeng et al. (1994) *Nucleic Acids Res.* 22:4381-4385; Hubank and Schatz (1994) *Nucleic Acids Res.* 22:5640-5648). Also recently, a microarray technology (DNA chips) developed by Affymetrix (Santa Clara, CA) has been used as a powerful tool to simultaneously identify a large number of differentially 10 expressed genes in a biological sample. Each of these methods can be employed in the present invention and is hereby incorporated by reference in entirety.

By using the Affymetrix chips (GeneChip Human Genome U133 Set), the inventors of the present invention identified two clusters of differentially expressed marker sequences that have shown at least a two-fold change (either increase or decrease) in expression level in 15 biological samples from tumor cells and/or tissue, e.g., colon cancer-derived cells and/or tissue, relative to the expression level in samples from normal cells and/or tissue, e.g., normal colon tissue and/or normal non-colon tissue. Table 1 describes 47 marker sequences that are over-expressed (up-regulated) in tumor cells and/or tissue, e.g., colon cancer-derived cells and/or tissue.

20 **Table 1. Over-expressed Marker sequences**

SEQ ID NO	Gene Symbol & Locus ID	Accession Number	Type	Corresponding Protein Accession Number	Protein SEQ ID NO
1	KRT23, 25984	NM_015515	RNA	NP_056330	94
2	REG1A, 5967	NM_002909	RNA	NP_002900	95
3	REG1B, 5968	NM_006507	RNA	NP_006498	96
4	DPEP1, 1800	NM_004413	RNA	NP_004404	97

5	IL8, 3576	NM_000584	RNA	NP_00575	98
6	MMP1, 4312	NM_002421	RNA	NP_002412	99
7	MMP7, 4316	NM_002423	RNA	NP_002414	100
8	SSP1, 6696	NM_000582	RNA	NP_000573	101
9	CXCL10, 3627	NM_001565	RNA	NP_001556	102
10	SULF1, 23213	NM_015170	RNA	NP_055985	103
11	COL5A2, 1290	NM_000393	RNA	NP_000384	104
12	CXCL1, 2919	NM_001511	RNA	NP_001502	105
13	CCL18, 6362	NM_002988	RNA	NP_002979	106
14	CDH11, 1009	NM_001797	RNA	NP_001788	107
15	BST2, 684	NM_004335	RNA	NP_004326	108
16	C20orf97, 57761	NM_021158	RNA	NP_066981	109
17	THBS2, 7058	NM_003247	RNA	NP_003238	110
18	G1P3, 2537	NM_022873	RNA	NP_075011	111
19	CKTSF1B1, 26585	NM_013372	RNA	NP_037504	112
20	MMP9, 4318	NM_004994	RNA	NP_004985	113
21	RAB31, 11031	NM_006868	RNA	NP_006859	114
22	DD96, 10158	NM_005764	RNA	NP_005755	115

23	SUPT4H1, 6827	NM_003168	RNA	NP_003159	116
24	FXVD5, 53827	NM_014164	RNA	NP_054883	117
25	CSPG2, 1462	NM_004385	RNA	NP_004376	118
26	LAPTM4B, 55353	NM_018407	RNA	NP_060877	119
27	SOX4, 6659	NM_003107	RNA	NP_003098	120
28	SORD, 6652	NM_003104	RNA	NP_003095	121
29	MMP12, 4321	NM_002426	RNA	NP_002417	122
30	UBD, 10537	NM_006398	RNA	NP_006389	123
31	DKFZp564I192 2, 25878	NM_015419	RNA	NP_056234	124
32	COL1A1, 1277	NM_000088	RNA	NP_000079	125
33	PLAB, 9518	NM_004864	RNA	NP_004855	126
34	SCD, 6319	NM_005063	RNA	NP_005054	127
35	CCL20, 6364	NM_004591	RNA	NP_004582	128
36	BACE2, 25825	NM_012105	RNA	NP_036237	129
37	GTF3A, 2971	NM_002097	RNA	NP_002088	130
38	C20orf42, 55612	NM_017671	RNA	NP_060141	131
39	OSF-2, 10631	NM_006475	RNA	NP_006466	132
40	SPARC, 6678	NM_003118	RNA	NP_003109	133

41	TGFBI, 7045	NM_000358	RNA	NP_000349	134
42	FN1, 2335	NM_002026	RNA	NP_002017	135
43	COL1A2, 1278	NM_000089	RNA	NP_000080	136
44	S100A11, 6282	NM_005620	RNA	NP_005611	137
45	IFITM1, 8519	NM_003641	RNA	NP_003632	138
46		AF130095	RNA	AAG35520	139
47	COL3A1, 1281	NM_000090	RNA	NP_000081	140

Accordingly, the present invention provides marker sequences in Table 1 that are over-expressed by at least about 2 fold, at least about 5 fold, at least about 10 fold, at least about 20 fold, or at least about 50 fold. In one embodiment, the present invention encompasses marker sequences that are over-expressed (up-regulated) in tumor cells and/or tissue, especially in colon cancer cells and/or tissue and/or colon cancer-derived cell lines. In a preferred embodiment, the marker sequences are over-expressed (up-regulated) by at least about 2 fold, at least about 5 fold, at least about 10 fold, at least about 20 fold, or at least about 50 fold.

Table 2 describes 46 marker sequences that are under-expressed (down-regulated) in tumor cells and/or tissue, e.g., colon cancer-derived cells and/or tissue.

**Table 2 Under-expressed Marker sequences**

SEQ ID NO	Gene Symbol & Locus ID	Accession Number	Type	Corresponding Protein Accession Number	Protein SEQ ID NO
48	GCG, 2641	NM_002054	RNA	NP_002045	141
49	SPINK5, 11005	NM_006846	RNA	NP_006837	142
50	ANPEP, 290	NM_001150	RNA	NP_001141	143

51	AQP8, 343	NM_001169	RNA	NP_001160	144
52	GUCA2B, 2981	NM_007102	RNA	NP_009033	145
53	CLCA4, 22802	NM_012128	RNA	NP_036260	146
54	PRV1, 57126	NM_020406	RNA	NP_065139	147
55	EKI1, 55500	NM_018638	RNA	NP_061108	148
56	FLJ22595, 80117	NM_025047	RNA	NP_079323	149
57	UGT2B15	NM_001076	RNA	NP_001067	150
58	CEACAM7, 1087	NM_006890	RNA	NP_008821	151
59	CHGA, 1113	NM_001275	RNA	NP_001266	152
60	HPGD, 3248	NM_000860	RNA	NP_000851	153
61	MGC4172, 79154	NM_024308	RNA	NP_077284	154
62	CA4, 762	NM_000717	RNA	NP_000708	155
63	IL1R2, 7850	NM_004633	RNA	NP_004624	156
64	FLJ20127, 54827	NM_017678	RNA	NP_060148	157
65	MS4A12, 54860	NM_017716	RNA	NP_060186	158
66	EMP1, 2012	NM_001423	RNA	NP_001414	159
67	SLC4A4, 8671	NM_003759	RNA	NP_003750	160



68	ADH1C, 126	NM_000669	RNA	NP_000660	161
69	CEACAM1, 634	NM_001712	RNA	NP_001703	162
70	MAWBP, 64081	NM_022129	RNA	NP_071412	163
71	PCK1, 5105	NM_002591	RNA	NP_002582	164
72	UGT2B17, 7367	NM_001077	RNA	NP_001068	165
73	HSD17B2	NM_002153	RNA	NP_002144	166
74	LOC63928, 63928	NM_022097	RNA	NP_071380	167
75	RDHL, 10170	NM_005771	RNA	NP_005762	168
76	GUCA1B, 2979	NM_002098	RNA	NP_002089	169
77	FHL1, 2273	NM_001449	RNA	NP_001440	170
78	ADAMDEC1, 27299	NM_014479	RNA	NP_055294	171
79	SPINK4, 27290	NM_014471	RNA	NP_055286	172
80	CA1, 759	NM_001738	RNA	NP_001729	173
81	SGK, 6446	NM_005627	RNA	NP_005618	174
82	CKB, 1152	NM_001823	RNA	NP_001814	175
83	SLC26A2, 1836	NM_000112	RNA	NP_000103	176
84	RNAHP, 11325	NM_007372	RNA	NP_031398	177
85	MUC2, 4583	NM_002457	RNA	NP_002448	178

86	HMGCS2, 3258	NM_005518	RNA	NP_005509	179
87	CLCA1, 1179	NM_001285	RNA	NP_001276	180
88	MT1F, 4494	NM_005949	RNA	NP_005940	181
89	CA2, 760	NM_000067	RNA	NP_000058	182
90	MT1H, 4496	NM_005951	RNA	NP_005942	183
91	MT1G, 4495	NM_005950	RNA	NP_005941	184
92	ZG16, 123887	NM_152338	RNA	NP_689551	185
93	MT1X, 4501	NM_005952	RNA	NP_005943	186

Accordingly, the present invention provides marker sequences in Table 2 that are under-expressed (down-regulated) by at least about 2 fold, at least about 5 fold, at least about 10 fold, at least about 20 fold, or at least about 50 fold. In one embodiment, the present invention encompasses marker sequences that are over-expressed (down-regulated) in tumor cells and/or tissue, especially in colon cancer cells and/or tissue and/or colon cancer-derived cell lines. In a preferred embodiment, the marker sequences are under-expressed (down-regulated) by at least about 2 fold, at least about 5 fold, at least about 10 fold, at least about 20 fold, or at least about 50 fold.

The present invention also encompasses sequences which differ from the marker sequences identified in Tables 1 and 2, but which produce the same phenotypic effect, for example, an allelic variant.

The present invention further encompasses polynucleotides which are at least about 85%, or at least about 90%, or more preferably equal to or greater than about 95% identical to the sequences of the RNA transcripts or cDNAs of the marker sequences. Sequence identity as used herein refers to the proportion of base matches between two nucleic acid sequences or the proportion amino acid matches between two amino acid sequences. When sequence homology is

expressed as a percentage, e.g., 50%, the percentage denotes the proportion of matches over the length of sequence from one sequence that is compared to some other sequence.

The identification of marker sequences that are differentially expressed in tumor cells and/or tissue as compared to normal cells and/or tissue, has applications in a number of ways.

5 For example, diagnosis may be done or confirmed by comparing patient samples with the known expression profiles. Similarly, a particular treatment may be evaluated, such evaluation including whether a therapeutic treatment improves the long-term prognosis in a particular patient. Furthermore, the gene expression profiles or individual genes allow screening drug candidates. These methods can also be done at protein level. That is, protein expression levels  
10 of the marker sequences associated with the tumor or pre-malignant conditions can be evaluated for diagnostic and prognostic purposes or for screening candidate composition for inhibiting tumors or pre-malignant conditions.

#### IV Primers and probes

The nucleic acid sequences of the identified marker sequences that are differentially  
15 expressed in tumor cells and/or tissue will further allow for the generation of probes and primers designed to detect transcripts or genomic sequences corresponding to one or more marker sequences of the present invention. The probe/primer is typically used as one or more substantially purified oligonucleotides. The primer/probe may comprise a portion or all of the sequences listed in SEQ ID NOs: 1-93, or sequences complementary thereto, or sequences which  
20 hybridize under stringent conditions to a portion or all of SEQ ID NOs: 1-93. In one embodiment, the probe/primer can comprise a sequence that hybridizes under stringent conditions to at least about 7, preferably about 12, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400, or more consecutive nucleotides of SEQ ID NOs: 1-93 of the present invention. As used herein, the term "hybridizes under stringent  
25 conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least about 75% (about 80%, 85%, preferably about 90%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of  
30 stringent hybridization conditions for annealing two single-stranded DNA each of which is at least about 100 bases in length and/or for annealing a single-stranded DNA and a single-stranded

RNA each of which is at least about 100 bases in length, are hybridization in 6 x sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 x SSC, 0.1% SDS at 50-65°C. Further preferred hybridization conditions are taught in Lockhart, et al., *Nature Biotechnology*, 14:1675-1680 (1996); Breslauer, et al., *Proc. Natl. Acad. Sci. USA*, 83:3746-3750 (1986); Van Ness, et al., *Nucleic Acids Research*, 19: 5143-5151 (1991); McGraw, et al., *BioTechniques*, 8: 674-678 (1990); and Milner, et al., *Nature Biotechnology*, 15: 537-541 (1997), all expressly incorporated by reference.

In another embodiment, the probe/primer can comprise a sequence that hybridizes under moderately stringent conditions to at least about 7, preferably 12, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400, or more consecutive nucleotides of SEQ ID NOs: 1-93 of the present invention. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides include prewashing in a solution of 5 x SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C to 60°C, 5 x SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2 x, 0.5 x, and 0.2 x SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed.

In particular, these probes are useful because they provide a method for detecting mutations in wild-type marker sequences of the present invention. Nucleic acid probes which are complementary to a wild-type marker sequence of the present invention and can form mismatches with mutant marker sequences are provided, allowing for detection by enzymatic or chemical cleavage or by shifts in electrophoretic mobility. Likewise, probes based on the subject sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins, for use, for example, in prognostic or diagnostic assays.

Nucleic acid probes may be generated using techniques which are well known to those of skill in the art (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989), or *Current Protocols in Molecular Biology*, F. Ausubel et al., ed. Greene Publishing and Wiley-Interscience, New York (1987).

In order to measure the hybridization of a nucleic acid probe to a target sequence in a biological sample, the probe is preferably labeled with a detectable label. In preferred embodiments, the probe further comprises a label group attached thereto and able to be detected. Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (e.g., Dynabeads<sup>TM</sup>), fluorescent dyes (e.g., fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., <sup>3</sup>H, <sup>125</sup>I, <sup>35</sup>S, <sup>14</sup>C, or <sup>32</sup>P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241.

Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

The labels may be incorporated into a nucleic acid probe by any of a number of means well known to those of skill in the art. However, in a preferred embodiment, the label is simultaneously incorporated into the probe during an amplification step in the preparation of the probe polynucleotides. Thus, for example, polymerase chain reaction (PCR), or other amplification reaction, with labeled primers or labeled nucleotides will provide a labeled amplification product, and thus a labeled probe.

Alternatively, a label may be added directly to the probe. Means of attaching labels to polynucleotides are well known to those of skill in the art and include, for example nick translation or end-labeling (e.g. with a labeled RNA) and subsequent attachment (ligation) of a polynucleotide linker joining the sample polynucleotide to a label (e.g., a fluorophore).

In a preferred embodiment, the fluorescent modifications are by cyanine dyes e.g. Cy-3/Cy-5 dUTP, Cy-3/Cy-5 dCTP (Amersham Pharmacia) or alexa dyes (Khan, J., Simon, R., Bittner, M., Chen, Y., Leighton, S. B., Pohida, T., Smith, P. D., Jiang, Y., Gooden, G. C., Trent, J. M. & Meltzer, P. S. (1998) *Cancer Res.* 58, 50095013.).

5     V     Polynucleotide composition

Full-length cDNA molecules comprising the disclosed nucleic acids of the marker sequences, useful for the generation of probes, primers, or for transcription to produce the protein of the marker sequences, or antibodies thereto may be obtained as follows. The nucleic acid sequences of the marker sequences or a portion thereof comprising at least approximately 8,  
10 preferably about 12, preferably about 15, preferably about 25, more preferably about 40 nucleotides up to the full length of the sequence of SEQ ID NOs: 1-93, or a sequence complementary thereto, may be used as a hybridization probe to detect hybridizing members of a cDNA library using probe design methods, cloning methods, and clone selection techniques as described in U.S. Patent No. 5,654,173, "Secreted Proteins and Polynucleotides Encoding  
15 Them," incorporated herein by reference. Libraries of cDNA may be made from selected tissues, such as normal or tumor tissue, or from tissues of a mammal treated with, for example, a pharmaceutical compound. Preferably, the tissue is the same as that used to generate the nucleic acids, as both the nucleic acid and the cDNA represent expressed genes. Alternatively, many cDNA libraries are available commercially. (Sambrook et al., *Molecular Cloning: A Laboratory  
20 Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). The choice of cell type for library construction may be made after the identity of the protein encoded by the nucleic acid-related gene is known. This will indicate which tissue and cell types are likely to express the related gene, thereby containing the mRNA for generating the cDNA.

Members of the library that are larger than the nucleic acid, and preferably that contain  
25 the whole sequence of the native message, may be obtained. To confirm that the entire cDNA has been obtained, RNA protection experiments may be performed as follows. Hybridization of a full-length cDNA to an mRNA may protect the RNA from RNase degradation. If the cDNA is not full length, then the portions of the mRNA that are not hybridized may be subject to RNase degradation. This may be assayed, as is known in the art, by changes in electrophoretic mobility  
30 on polyacrylamide gels, or by detection of released monoribonucleotides. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring

Harbor, NY 1989). In order to obtain additional sequences 5' to the end of a partial cDNA, 5' RACE (*PCR Protocols: A Guide to Methods and Applications* (Academic Press, Inc. 1990)) may be performed.

5 Genomic DNAs of the marker sequences may be isolated using nucleic acids in a manner similar to the isolation of full-length cDNAs. Briefly, the nucleic acids, or portions thereof, may be used as probes to libraries of genomic DNA. Preferably, the library is obtained from the cell type that was used to generate the nucleic acids. Most preferably, the genomic DNA is obtained from the biological material described herein in the Example. Such libraries may be in vectors suitable for carrying large segments of a genome, such as P1 or YAC, as described in detail in 10 Sambrook et al., pages 9.4-9.30. In addition, genomic sequences can be isolated from human BAC libraries, which are commercially available from Research Genetics, Inc., Huntsville, Alabama, USA, for example. In order to obtain additional 5' or 3' sequences, chromosome walking may be performed, as described in Sambrook et al., such that adjacent and overlapping fragments of genomic DNA are isolated. These may be mapped and pieced together, as is 15 known in the art, using restriction digestion enzymes and DNA ligase.

Using the nucleic acids of the invention, corresponding full length genes can be isolated using both classical and PCR methods to construct and probe cDNA libraries. Using either method, Northern blots, preferably, may be performed on a number of cell types to determine which cell lines express the gene of interest at the highest rate.

20 Classical methods of constructing cDNA libraries in Sambrook et al., *supra*. With these methods, cDNA can be produced from mRNA and inserted into viral or expression vectors. Typically, libraries of mRNA comprising poly(A) tails can be produced with poly(T) primers. Similarly, cDNA libraries can be produced using the instant marker sequences or portions thereof as primers.

25 PCR methods may be used to amplify the members of a cDNA library that comprise the desired insert. In this case, the desired insert may contain sequence from the full length cDNA that corresponds to the sequence encoding Reg1 $\alpha$ . Such PCR methods include gene trapping and RACE methods.

Gene trapping may entail inserting a member of a cDNA library into a vector. The vector then may be denatured to produce single stranded molecules. Next, a substrate-bound probe, such as biotinylated oligonucleotide, may be used to trap cDNA inserts of interest. Biotinylated probes can be linked to an avidin-bound solid substrate. PCR methods can be used to amplify the trapped cDNA. To trap sequences corresponding to the full length genes, the labeled probe sequence may be based on the nucleic acid of SEQ ID NOs: 1-93, or a sequence complementary thereto. Random primers or primers specific to the library vector can be used to amplify the trapped cDNA. Such gene trapping techniques are described in Gruber et al., PCT WO 95/04745 and Gruber et al., U.S. Pat. No. 5,500,356. Kits are commercially available to perform gene trapping experiments from, for example, Life Technologies, Gaithersburg, Maryland, USA.

“Rapid amplification of cDNA ends,” or RACE, is a PCR method of amplifying cDNAs from a number of different RNAs. The cDNAs may be ligated to an oligonucleotide linker and amplified by PCR using two primers. One primer may be based on sequence from the instant nucleic acids, for which full length sequence is desired, and a second primer may comprise a sequence that hybridizes to the oligonucleotide linker to amplify the cDNA. A description of this method is reported in PCT Pub. No. WO 97/19110.

In preferred embodiments of RACE, a common primer may be designed to anneal to an arbitrary adaptor sequence ligated to cDNA ends (Apte and Siebert, *Biotechniques* 15:890-893 (1993); Edwards et al., *Nuc. Acids Res.* 19:5227-5232 (1991)). When a single gene-specific RACE primer is paired with the common primer, preferential amplification of sequences between the single gene specific primer and the common primer occurs. Commercial cDNA pools modified for use in RACE are available.

Once the full-length cDNA or gene is obtained, DNA encoding variants can be prepared by site-directed mutagenesis, described in detail in Sambrook 15.3-15.63. The choice of codon or nucleotide to be replaced can be based on the disclosure herein on optional changes in amino acids to achieve altered protein structure and/or function.

As an alternative method to obtaining DNA or RNA from a biological material, such as serum, nucleic acid comprising nucleotides having the sequence of one or more nucleic acids of the invention can be synthesized. Thus, the invention encompasses nucleic acid molecules ranging in length from about 8 nucleotides (corresponding to at least 12 contiguous nucleotides



which hybridize under stringent conditions to or are at least 80% identical to the nucleic acid sequence of SEQ ID NOs:1-93, or a sequence complementary thereto) up to a maximum length suitable for one or more biological manipulations, including replication and expression, of the nucleic acid molecule. The invention includes but is not limited to (a) nucleic acid comprising the size of the full marker genes, or a sequence complementary thereto; (b) the nucleic acid of (a) also comprising at least one additional gene, operably linked to permit expression of a fusion protein; (c) an expression vector comprising (a) or (b); (d) a plasmid comprising (a) or (b); and (e) a recombinant viral particle comprising (a) or (b).

The sequence of a nucleic acid of the present invention is not limited and can be any sequence of A, T, G, and/or C (for DNA) and A, U, G, and/or C (for RNA) or modified bases thereof, including inosine and pseudouridine. The choice of sequence will depend on the desired function and can be dictated by coding regions desired, the intron-like regions desired, and the regulatory regions desired.

In various embodiments described above, the polynucleotides of the present invention can be modified at the base moiety, sugar moiety, or phosphate backbone to improve the stability, hybridization, or solubility of the molecule. For example, detectable markers (avidin, biotin, radioactive elements, fluorescent tags and dyes, energy transfer labels, energy-emitting labels, binding partners, etc.) or moieties which improve hybridization, detection, and/or stability can be attached to the polynucleotides. The polynucleotides can also be attached to solid supports, e.g., nitrocellulose, magnetic or paramagnetic microspheres (e.g., as described in U.S. Pat. Nos. 5,411,863; 5,543,289; for instance, comprising ferromagnetic, super-magnetic, paramagnetic, superparamagnetic, iron oxide and polysaccharide), nylon, agarose, diazotized cellulose, latex solid microspheres, polyacrylamides, etc., according to a desired method. See, e.g., U.S. Pat. Nos. 5,470,967, 5,476,925, and 5,478,893.

Polynucleotide according to the present invention can be labeled according to any desired method. The polynucleotide can be labeled using radioactive tracers such as  $^{32}\text{P}$ ,  $^{35}\text{S}$ ,  $^3\text{H}$ , or  $^{14}\text{C}$ , to mention some commonly used tracers. The radioactive labeling can be carried out according to any method, such as, for example, terminal labeling at the 3' or 5' end using a radiolabeled nucleotide, polynucleotide kinase (with or without dephosphorylation with a phosphatase) or a ligase (depending on the end to be labeled). A non-radioactive labeling can also be used, combining a polynucleotide of the present invention with residues having immunological

properties (antigens, haptens), a specific affinity for certain recomounds (ligands), properties enabling detectable enzyme reactions to be completed (enzymes or coenzymes, enzyme substrates, or other substances involved in an enzymatic reaction), or characteristic physical properties, such as fluorescence or the emission or absorption of light at a desired wavelength, etc.

## VI Vectors and host cells

The present invention further provides vectors and plasmids useful for directing the expression of marker sequences, and further provides host cells which express the vectors and plasmids provided herein. Nucleic acid sequences useful for the expression from a vector or plasmid as described below include, but are not limited to any nucleic acid or gene sequence identified as being differentially regulated by the methods described above, and further include therapeutic nucleic acid molecules, such as antisense molecules. The host cell may be any prokaryotic or eukaryotic cell. Ligating the polynucleotide sequence into a gene construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures well known in the art.

### *Vectors*

There is a wide array of vectors known and available in the art that are useful for the expression of differentially expressed nucleic acid molecules according to the invention. The selection of a particular vector clearly depends upon the intended use the polypeptide encoded by the differentially expressed nucleic acid. For example, the selected vector must be capable of driving expression of the polypeptide in the desired cell type, whether that cell type be prokaryotic or eukaryotic. Many vectors comprise sequences allowing both prokaryotic vector replication and eukaryotic expression of operably linked gene sequences.

Vectors useful according to the invention may be autonomously replicating, that is, the vector, for example, a plasmid, exists extrachromosomally and its replication is not necessarily directly linked to the replication of the host cell's genome. Alternatively, the replication of the vector may be linked to the replication of the host's chromosomal DNA, for example, the vector may be integrated into the chromosome of the host cell as achieved by retroviral vectors.

Vectors useful according to the invention preferably comprise sequences operably linked to the sequence of interest (e.g., the marker sequences) that permit the transcription and translation of the sequence. Sequences that permit the transcription of the linked sequence of interest include a promoter and optionally also include an enhancer element or elements permitting the strong expression of the linked sequences. The term "transcriptional regulatory sequences" refers to the combination of a promoter and any additional sequences conferring desired expression characteristics (e.g., high level expression, inducible expression, tissue- or cell-type-specific expression) on an operably linked nucleic acid sequence.

The selected promoter may be any DNA sequence that exhibits transcriptional activity in the selected host cell, and may be derived from a gene normally expressed in the host cell or from a gene normally expressed in other cells or organisms. Examples of promoters include, but are not limited to the following: A) prokaryotic promoters - *E. coli* lac, tac, or trp promoters, lambda phage P<sub>R</sub> or P<sub>L</sub> promoters, bacteriophage T7, T3, Sp6 promoters, *B. subtilis* alkaline protease promoter, and the *B. stearothermophilus* maltogenic amylase promoter, etc.; B) eukaryotic promoters - yeast promoters, such as GAL1, GAL4 and other glycolytic gene promoters (see for example, Hitzeman et al., 1980, *J. Biol. Chem.* 255: 12073-12080; Alber & Kawasaki, 1982, *J. Mol. Appl. Gen.* 1: 419-434), LEU2 promoter (Martinez-Garcia et al., 1989, *Mol Gen Genet.* 217: 464-470), alcohol dehydrogenase gene promoters (Young et al., 1982, in *Genetic Engineering of Microorganisms for Chemicals*, Hollaender et al., eds., Plenum Press, NY), or the TPI1 promoter (U.S. Pat. No. 4,599,311); insect promoters, such as the polyhedrin promoter (U.S. Pat. No. 4,745,051; Vasuvedan et al., 1992, *FEBS Lett.* 311: 7-11), the P10 promoter (Vlak et al., 1988, *J. Gen. Virol.* 69: 765-776), the *Autographa californica* polyhedrosis virus basic protein promoter (EP 397485), the baculovirus immediate-early gene promoter gene 1 promoter (U.S. Pat. Nos. 5,155,037 and 5,162,222), the baculovirus 39K delayed-early gene promoter (also U.S. Pat. Nos. 5,155,037 and 5,162,222) and the OpMNPV immediate early promoter 2; mammalian promoters - the SV40 promoter (Subramani et al., 1981, *Mol. Cell. Biol.* 1: 854-864), metallothionein promoter (MT-1; Palmiter et al., 1983, *Science* 222: 809-814), adenovirus 2 major late promoter (Yu et al., 1984, *Nucl. Acids Res.* 12: 9309-21), cytomegalovirus (CMV) or other viral promoter (Tong et al., 1998, *Anticancer Res.* 18: 719-725), or even the endogenous promoter of a gene of interest in a particular cell type.

A selected promoter may also be linked to sequences rendering it inducible or tissue-specific. For example, the addition of a tissue-specific enhancer element upstream of a selected promoter may render the promoter more active in a given tissue or cell type. Alternatively, or in addition, inducible expression may be achieved by linking the promoter to any of a number of sequence elements permitting induction by, for example, thermal changes (temperature sensitive), chemical treatment (for example, metal ion- or IPTG-inducible), or the addition of an antibiotic inducing compound (for example, tetracycline).

Regulatable expression is achieved using, for example, expression systems that are drug inducible (e.g., tetracycline, rapamycin or hormone-inducible). Drug-regulatable promoters that are particularly well suited for use in mammalian cells include the tetracycline regulatable promoters, and glucocorticoid steroid-, sex hormone steroid-, ecdysone-, lipopolysaccharide (LPS)- and isopropylthiogalactoside (IPTG)-regulatable promoters. A regulatable expression system for use in mammalian cells should ideally, but not necessarily, involve a transcriptional regulator that binds (or fails to bind) nonmammalian DNA motifs in response to a regulatory agent, and a regulatory sequence that is responsive only to this transcriptional regulator.

Tissue-specific promoters may also be used to advantage in differentially expressed sequence-encoding constructs of the invention. A wide variety of tissue-specific promoters is known. As used herein, the term "tissue-specific" means that a given promoter is transcriptionally active (i.e., directs the expression of linked sequences sufficient to permit detection of the polypeptide product of the promoter) in less than all cells or tissues of an organism. A tissue specific promoter is preferably active in only one cell type, but may, for example, be active in a particular class or lineage of cell types (e.g., hematopoietic cells). A tissue specific promoter useful according to the invention comprises those sequences necessary and sufficient for the expression of an operably linked nucleic acid sequence in a manner or pattern that is essentially the same as the manner or pattern of expression of the gene linked to that promoter in nature. The following is a non-exclusive list of tissue specific promoters and literature references containing the necessary sequences to achieve expression characteristic of those promoters in their respective tissues; the entire content of each of these literature references is incorporated herein by reference. Examples of tissue specific promoters useful in the present invention are as follows:

Bowman et al., 1995 *Proc. Natl. Acad. Sci. USA* 92,12115-12119 describe a brain-specific transferrin promoter; the synapsin I promoter is neuron specific (Schoch et al., 1996 *J. Biol. Chem.* 271, 3317-3323); the nestin promoter is post-mitotic neuron specific (Uetsuki et al., 1996 *J. Biol. Chem.* 271, 918-924); the neurofilament light promoter is neuron specific (Charron et al., 1995 *J. Biol. Chem.* 270, 30604-30610); the acetylcholine receptor promoter is neuron specific (Wood et al., 1995 *J. Biol. Chem.* 270, 30933-30940); and the potassium channel promoter is high-frequency firing neuron specific (Gan et al., 1996 *J. Biol. Chem.* 271, 5859-5865). Any tissue specific transcriptional regulatory sequence known in the art may be used to advantage with a vector encoding a differentially expressed nucleic acid sequence obtained from an animal subjected to pain.

In addition to promoter/enhancer elements, vectors useful according to the invention may further comprise a suitable terminator. Such terminators include, for example, the human growth hormone terminator (Palmiter et al., 1983, *supra*), or, for yeast or fungal hosts, the TPII (Alber & Kawasaki, 1982, *supra*) or ADH3 terminator (McKnight et al., 1985, *EMBO J.* 4: 2093-2099).

Vectors useful according to the invention may also comprise polyadenylation sequences (e.g., the SV40 or Ad5E1b poly(A) sequence), and translational enhancer sequences (e.g., those from Adenovirus VA RNAs). Further, a vector useful according to the invention may encode a signal sequence directing the recombinant polypeptide to a particular cellular compartment or, alternatively, may encode a signal directing secretion of the recombinant polypeptide.

a. Plasmid vectors.

Any plasmid vector that allows expression of a coding sequence of interest (e.g., the coding sequence of Reg1 $\alpha$ ) in a selected host cell type is acceptable for use according to the invention. A plasmid vector useful in the invention may have any or all of the above-noted characteristics of vectors useful according to the invention. Plasmid vectors useful according to the invention include, but are not limited to the following examples: Bacterial - pQE70, pQE60, pQE-9 (Qiagen) pBs, phagescript, psiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia); Eukaryotic - pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other plasmid or vector may be used as long as it is replicable and viable in the host.

b. Bacteriophage vectors.

There are a number of well known bacteriophage-derived vectors useful according to the invention. Foremost among these are the lambda-based vectors, such as Lambda Zap II or Lambda-Zap Express vectors (Stratagene) that allow inducible expression of the polypeptide encoded by the insert. Others include filamentous bacteriophage such as the M13-based family of vectors.

c. Viral vectors.

A number of different viral vectors are useful according to the invention, and any viral vector that permits the introduction and expression of one or more of the polynucleotides of the invention in cells is acceptable for use in the methods of the invention. Viral vectors that can be used to deliver foreign nucleic acid into cells include but are not limited to retroviral vectors, adenoviral vectors, adeno-associated viral vectors, herpesviral vectors, and Semliki forest viral (alphaviral) vectors. Defective retroviruses are well characterized for use in gene transfer (for a review see Miller, A.D. (1990) *Blood* 76:271). Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in *Current Protocols in Molecular Biology*, Ausubel, F.M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals.

In addition to retroviral vectors, Adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle (see for example Berkner et al., 1988, *BioTechniques* 6:616; Rosenfeld et al., 1991, *Science* 252:431-434; and Rosenfeld et al., 1992, *Cell* 68:143-155). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are well known to those skilled in the art. Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a productive life cycle. (For a review see Muzyczka et al., 1992, *Curr. Topics in Micro. and Immunol.* 158:97-129). An AAV vector such as that described in Traschin et al. (1985, *Mol. Cell. Biol.* 5:3251-3260) can be used to introduce nucleic acid into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors (see, for example,

Hermonat et al., 1984, *Proc. Natl. Acad. Sci. USA* 81: 6466-6470; and Traschin et al., 1985, *Mol. Cell. Biol.* 4: 2072-2081).

#### *Host cells*

Any cell into which a recombinant vector carrying a gene of interest (e.g., a sequence  
5 encoding the marker sequences) may be introduced and wherein the vector is permitted to drive  
the expression of the peptide encoded by the differentially expressed sequence is useful  
according to the invention. Any cell in which a differentially expressed molecule of the  
invention may be expressed and preferably detected is a suitable host, wherein the host cell is  
preferably a mammalian cell and more preferably a human cell. Vectors suitable for the  
10 introduction of nucleic acid sequences to host cells from a variety of different organisms, both  
prokaryotic and eukaryotic, are described herein above or known to those skilled in the art.

Host cells may be prokaryotic, such as any of a number of bacterial strains, or may be  
eukaryotic, such as yeast or other fungal cells, insect or amphibian cells, or mammalian cells  
including, for example, rodent, simian or human cells. Cells may be primary cultured cells, for  
15 example, primary human fibroblasts or keratinocytes, or may be an established cell line, such as  
NIH3T3, 293T or CHO cells. Further, mammalian cells useful in the present invention may be  
phenotypically normal or oncogenically transformed. It is assumed that one skilled in the art can  
readily establish and maintain a chosen host cell type in culture.

#### *Introduction of vectors to host cells.*

20 Vectors useful in the present invention may be introduced to selected host cells by any of  
a number of suitable methods known to those skilled in the art. For example, vector constructs  
may be introduced to appropriate bacterial cells by infection, in the case of *E. coli* bacteriophage  
vector particles such as lambda or M13, or by any of a number of transformation methods for  
plasmid vectors or for bacteriophage DNA. For example, standard calcium-chloride-mediated  
25 bacterial transformation is still commonly used to introduce naked DNA to bacteria (Sambrook  
et al., 1989, *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor Laboratory Press,  
Cold Spring Harbor, NY), but electroporation may also be used (Ausubel et al., 1988, *Current  
Protocols in Molecular Biology*, (John Wiley & Sons, Inc., NY, NY)).

For the introduction of vector constructs to yeast or other fungal cells, chemical transformation methods are generally used (e.g. as described by Rose et al., 1990, *Methods in Yeast Genetics*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY). For transformation of *S. cerevisiae*, for example, the cells are treated with lithium acetate to achieve transformation efficiencies of approximately  $10^4$  colony-forming units (transformed cells)/ $\mu\text{g}$  of DNA. Transformed cells are then isolated on selective media appropriate to the selectable marker used. Alternatively, or in addition, plates or filters lifted from plates may be scanned for GFP fluorescence to identify transformed clones.

For the introduction of vectors comprising a sequence of interest to mammalian cells, the method used will depend upon the form of the vector. Plasmid vectors may be introduced by any of a number of transfection methods, including, for example, lipid-mediated transfection ("lipofection"), DEAE-dextran-mediated transfection, electroporation or calcium phosphate precipitation. These methods are detailed, for example, in *Current Protocols in Molecular Biology* (Ausubel et al., 1988, John Wiley & Sons, Inc., NY, NY).

Lipofection reagents and methods suitable for transient transfection of a wide variety of transformed and non-transformed or primary cells are widely available, making lipofection an attractive method of introducing constructs to eukaryotic, and particularly mammalian cells in culture. For example, LipofectAMINE<sup>TM</sup> (Life Technologies) or LipoTaxi<sup>TM</sup> (Stratagene) kits are available. Other companies offering reagents and methods for lipofection include Bio-Rad Laboratories, CLONTECH, Glen Research, InVitrogen, JBL Scientific, MBI Fermentas, PanVera, Promega, Quantum Biotechnologies, Sigma-Aldrich, and Wako Chemicals USA.

Following transfection with a vector of the invention, eukaryotic (e.g., human) cells successfully incorporating the construct (intra- or extrachromosomally) may be selected, as noted above, by either treatment of the transfected population with a selection agent, such as an antibiotic whose resistance gene is encoded by the vector, or by direct screening using, for example, FACS of the cell population or fluorescence scanning of adherent cultures. Frequently, both types of screening may be used, wherein a negative selection is used to enrich for cells taking up the construct and FACS or fluorescence scanning is used to further enrich for cells expressing differentially expressed polynucleotides or to identify specific clones of cells, respectively. For example, a negative selection with the neomycin analog G418 (Life Technologies, Inc.) may be used to identify cells that have received the vector, and fluorescence



scanning may be used to identify those cells or clones of cells that express the vector construct to the greatest extent.

## VII Polypeptides

One aspect of the present invention pertains to isolated polypeptides which correspond to individual marker sequences of the present invention, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a polypeptide encoded by a nucleic acid marker sequence of the present invention. In one embodiment, the native polypeptide encoded by a marker sequence can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, polypeptides encoded by a nucleic acid marker sequence of the invention are produced by recombinant DNA techniques. Alternative to recombinant expression, a polypeptide encoded by a nucleic acid marker sequence of the invention can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, i.e., culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, i.e., it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a polypeptide encoded by a nucleic acid marker sequence of the invention include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the protein encoded by the nucleic acid marker sequence (e.g., the amino acid sequence listed in the GenBank and IMAGE Consortium database records described herein), which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding protein. A biologically active portion of a protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of a polypeptide of the invention.

The polypeptides may contain amino acid substitutions, deletions or insertions made on the basis of similarity in polarity, charge, solubility, hydrophobicity, and/or the amphipathic nature of the residues involved. Such substitutions may be conservative in nature when the substituted residue has structural or chemical properties similar to the original residue (e.g., replacement of leucine with isoleucine or valine) or they may be nonconservative when the replacement residue is radically different (e.g., a glycine replaced by a tryptophan). Computer programs included in LASERGENE software (DNASTAR, Madison, Wis.) and algorithms included in RasMol software (University of Massachusetts, Amherst, Mass.) may be used to help determine which and how many amino acid residues in a particular portion of the protein may be substituted, inserted, or deleted without abolishing biological or immunological activity.

The present invention also provides chimeric or fusion proteins corresponding to a marker sequence of the invention. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a polypeptide encoded by a nucleic acid marker sequence of the invention operably linked to a heterologous polypeptide (i.e., a polypeptide other than the polypeptide encoded by the nucleic acid marker sequence). Within the fusion protein, the term "operably linked" is intended to indicate that the polypeptide of the invention and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the polypeptide of the invention.

One useful fusion protein is a GST fusion protein in which a polypeptide encoded by a nucleic acid marker sequence of the invention is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

5 In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a polypeptide encoded by a nucleic acid marker sequence of the invention can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel et al., ed., *Current Protocols in Molecular*  
10 *Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, Calif.). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook et al., *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, N.J.). A signal sequence can be used to facilitate  
15 secretion and isolation of the secreted protein or other proteins of interest.

In addition to recombinant production, proteins or portions thereof may be produced manually, using solid-phase techniques (Stewart et al. (1969) *Solid-Phase Peptide Synthesis*, WH Freeman, San Francisco, Calif.; Merrifield (1963) *J Am Chem Soc* 5:2149-2154), or using machines such as the 431A peptide synthesizer (Applied Biosystems (ABI), Foster City, Calif.).  
20 Proteins produced by any of the above methods may be used as pharmaceutical compositions to treat disorders associated with null or inadequate expression of the genomic sequence.

## VIII Antibodies

Another aspect of the present invention pertains to antibodies directed to polypeptides and fragments thereof of the marker sequences of the present invention. An isolated polypeptide  
25 encoded by a nucleic acid marker sequence of the present invention, or fragment thereof, can be used as an immunogen to generate antibodies using standard techniques. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, or chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic antibodies, or other  
30 epitope binding polypeptide. Preferably, an antibody, useful in the present invention for the

detection of the individual marker sequences (and optionally at least one additional colon cancer-specific marker), is a human antibody or fragment thereof, including scFv, Fab, Fab', F(ab'), Fd, single chain antibody, or Fv. Antibodies, useful in the invention may include a complete heavy or light chain constant region, or a portion thereof, or an absence thereof. An antibody, useful in the invention, may be obtained from an art recognized host, such as rabbit, mouse, rat, donkey, sheep, goat, guinea pig, camel, horse, or chicken. In one embodiment, an antibody, useful in the invention can be a humanized antibody, in which amino acids have been replaced in the non-antigen binding regions in order to more closely resemble a human antibody, while still retaining the original binding ability. Methods for making humanized antibodies are described in Teng et al., 1983, *Proc. Natl. Acad. Sci. USA* 80: 7308-7312; Kozbor et al., 1983, *Immunology Today* 4: 7279; Olsson et al., 1982, *Meth. Enzymol.* 92: 3-16; WO 92/06193; EP 0239400.

Antibodies of the present invention may be monospecific, dispecific, trispecific, or of greater multispecificity. As such, the individual marker sequences useful for the detection of cancer may be detected with separate antibodies, or may be detected with the same antibody. Alternatively, a multispecific antibody may exhibit different specificities for different epitopes on the same protein (e.g., different epitopes on a marker sequence). While specificity of an antibody useful in the present invention to one or more additional cancer-specific markers is preferred, antibodies that bind polypeptides with at least 95%, 90%, 85%, 75%, 65%, 55%, and at least 50% identity to a polypeptide useful in the present invention for the detection of cancer, particularly colon cancer are also included in the present invention. Also encompassed in the present invention are antibodies which bind to polypeptide molecules which are encoded by one or more nucleic acid sequences which are complementary to, or hybridize to the sequences of SEQ ID NOs: 1-93.

Antibodies of the present invention which are useful for the detection of colon cancer may further act as agonists or antagonists of the activity of the polypeptide molecules to which they bind, and may thus be useful as therapeutic molecules for the treatment or prevention of colon cancer.

An important, but not limiting, role of an antibody of the present invention is to provide for the purification, or detection of individual marker sequences in a patient sample, including both *in vitro* and *in vivo* detection methods. Antibodies useful for the detection of colon cancer as described herein do not have to be used alone, and can be fused to other polypeptides,

including a heterologous polypeptide at the N- or C-terminus of the antibody polypeptide sequence. For example, an antibody useful in the present invention may be fused with a detectable label to facilitate detection of the antibody when bound to a target polypeptide. Methods for detectably labeling an antibody polypeptide are known to those of skill in the art.

5 For the production of antibodies useful in the present invention, various hosts including goats, rabbits, rats, mice, etc., may be immunized by injection with the protein products (or any portion, fragment, or oligonucleotide thereof which retains immunogenic properties) of the candidate genes of the invention. Depending on the host species, various adjuvants may be used to increase the immunological response. Such adjuvants include but are not limited to Freund's, 10 mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum* are potentially useful human adjuvants.

Polyclonal antisera or monoclonal antibodies can be made using methods known in the 15 art. A mammal such as a mouse, hamster, or rabbit, can be immunized with an immunogenic form of a marker polypeptide, fragment, modified form thereof, or variant form thereof. Alternatively, an animal may be immunized with an immunogenic form of one or more additional colon cancer-specific marker polypeptides. Techniques for conferring 20 immunogenicity on such molecules include conjugation to carriers or other techniques well known in the art. For example, the immunogenic molecule can be administered in the presence of adjuvant as described above. Immunization can be monitored by detection of antibody titers in plasma or serum. Standard immunoassay procedures can be used with the immunogen as antigen to assess the levels and the specificity of antibodies. Following immunization, antisera can be obtained and, if desired, polyclonal antibodies isolated from the sera.

25 To produce monoclonal antibodies, antibody producing cells (lymphocytes) can be harvested from an immunized animal and fused with myeloma cells by standard somatic cell fusion procedures thus immortalizing these cells and yielding hybridoma cells. Such techniques are well known in the art (see, e.g., Kohler and Milstein, 1975, *Nature* 256: 495-497; Kozbor et al., 1983, *Immunol. Today* 4: 72, Cole et al., 1985, In *Monoclonal Antibodies in Cancer Therapy*, 30 Allen R. Bliss, Inc., pages 77-96). Additionally, techniques described for the production of

single-chain antibodies (U.S. Patent No. 4,946,778) can be adapted to produce antibodies according to the invention.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Pat. No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science* 246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

Antibody fragments which can specifically bind to a marker polypeptide of the present invention, or fragments thereof, modified forms thereof, and variants thereof, also may be generated by known techniques. For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. VH regions and FV regions can be expressed in bacteria using phage expression libraries (e.g., Ward et al., 1989, *Nature* 341: 544-546; Huse et al., 1989, *Science* 246: 1275-1281; McCafferty et al., 1990, *Nature* 348: 552-554).

Chimeric antibodies, i.e., antibody molecules that combine a non-human animal variable region and a human constant region also are within the scope of the invention. Chimeric antibody molecules include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. Standard methods may be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes the gene product of individual marker antigens of the invention (see, e.g., Morrison et al., 1985,

*Proc. Natl. Acad. Sci. USA* 81: 6851; Takeda et al., 1985, *Nature* 314: 452; U.S. Patent No. 4,816,567; U.S. Patent No. 4,816,397).

Antibodies of the invention may be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic  
5 treatment of human cancer patients, particularly those having cervical cancer. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide encoded by a nucleic acid marker sequences of the  
10 invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for  
15 producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Pat. No. 5,625,126; U.S. Pat. No. 5,633,425; U.S. Pat. No. 5,569,825; U.S. Pat. No. 5,661,016; and U.S. Pat. No. 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, Calif.), can be engaged to  
20 provide human antibodies directed against a selected antigen using technology similar to that described above.

An antibody directed against a polypeptide encoded by a nucleic acid marker sequence of the invention (e.g., a monoclonal antibody) can be used to isolate the polypeptide by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an  
25 antibody can be used to detect the marker sequence (e.g., in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker sequence. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (e.g. in an ovary-associated body fluid) as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the  
30 antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and

radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, .beta.-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{35}\text{S}$  or  $^3\text{H}$ .

Further, an antibody (or fragment thereof) can be conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), .sup.bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine). Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described in U.S. Pat. No. 4,676,980.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84; Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in



*Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

#### IX Detection of the marker sequences

5 In one aspect, the expression levels of the differentially expressed marker sequences are determined in normal and cancer cells and/or tissue, especially the colon cancer cells and/or tissue. In general, the present invention relates to methods of detecting a differentially-expressed nucleic acid sequence in a sample comprising nucleic acid. Such methods can comprise one or more of the following steps in any effective order, e.g., contacting said sample with  
10 polynucleotide probes under conditions effective for said probe to hybridize specifically to the nucleic acids of the marker sequences in said sample, and detecting the presence or absence of the nucleic acid marker sequences in said sample. In one preferred embodiment, said probes are polynucleotides designed to identify the marker sequences either in Table 1 or Table 2. The detection method can be applied to any sample, e.g., cultured primary, secondary, or established  
15 cell lines, tissue biopsy, blood, urine, stool, cerebral spinal fluid, and other bodily fluids, for any purpose.

In one embodiment, the probes of the individual and/or combinations of the marker sequences are applied to the samples obtained from both the normal and colon cancer cell lines, and the presence of the marker sequences are detected with the methods describes herein. In  
20 another embodiment, the probes of the individual and/or combinations of the marker sequences are applied to the samples obtained from both the normal and colon cancer tissue, and the amount of the marker sequences are detected with the methods describes herein. For example, one determination assay can employ the over-expressed marker sequences in combination with an the over-expressed or an under-expressed marker sequences. Moreover, the determination  
25 assay can employ a panel of at least two, or at least three, or at least four or more marker sequences, selected from both the over-expressed and the under-expressed marker sequences.

The methods of detecting the presence of the marker sequences can be carried out by any effective process, e.g., by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, in situ hybridization, etc.. When PCR based techniques are  
30 used, two or more probes are generally used. One probe can be specific for a defined sequence

which is characteristic of a selective polynucleotide, but the other probe can be specific for the selective polynucleotide, or specific for a more general sequence, e.g., a sequence such as polyA which is characteristic of mRNA, a sequence which is specific for a promoter, ribosome binding site, or other transcriptional features, a consensus sequence (e.g., representing a functional domain). For the former aspects, 5' and 3' probes (e.g., polyA, Kozak, etc.) are preferred which are capable of specifically hybridizing to the ends of transcripts. When PCR is utilized, the probes can also be referred to as "primers" in that they can prime a DNA polymerase reaction.

In addition to testing for the presence or absence of the marker polynucleotides, the present invention also relates to determining the amounts at which the marker sequences of the present invention are expressed in samples and determining the differential expression of such marker sequences in samples. Such methods can involve substantially the same steps as described above for presence/absence detection, e.g., contacting with probe, hybridizing, and detecting hybridized probe, but using more quantitative methods and/or comparisons to standards. The amount of hybridization between the probe and target can be determined by any suitable methods, e.g., PCR, RT-PCR, RACE PCR, Northern blot, polynucleotide microarrays, Rapid-Scan, etc., and includes both quantitative and qualitative measurements.

In one embodiment, reverse transcription PCR (RT-PCR) is performed using primers designed to specifically hybridize to a predetermined portion of the marker mRNA sequences isolated from a clinical sample. Generation of a PCR product by such a reaction is thus indicative of the presence of the marker sequences in the sample. The technique of designing primers for PCR amplification is well known in the art. Oligonucleotide primers and probes are about 5 to 100 nucleotides in length, ideally from about 17 to 40 nucleotides, although primers and probes of different length are of use. Primers for amplification are preferably about 17-25 nucleotides. Primers useful according to the invention are also designed to have a particular melting temperature ( $T_m$ ) by the method of melting temperature estimation. Commercial programs, including Oligo™ (MBI, Cascade, CO), Primer Design and programs available on the internet, including Primer3 and Oligo Calculator can be used to calculate a  $T_m$  of a nucleic acid sequence useful according to the invention. Preferably, the  $T_m$  of an amplification primer useful according to the invention, as calculated for example by Oligo Calculator, is preferably between about 45 and 65° C and more preferably between about 50 and 60° C. Preferably, the  $T_m$  of a probe useful according to the invention is 7° C higher than the  $T_m$  of the corresponding

amplification primers. It is preferred that, following generation of cDNA by RT-PCR, the cDNA fragment is cloned into an appropriate sequencing vector, such as a PCRII vector (TA cloning kit; Invitrogen). The identity of each cloned fragment is then confirmed by sequencing in both directions. It is expected that the sequence obtained from sequencing would be the same as the known sequences of the marker sequences as described herein.

Alternatively, the presence of mRNA sequences encoding the marker sequences may be detected by Northern analysis. Sequence confirmed cDNAs, that is, cDNAs encoding the marker sequences are used to produce  $^{32}\text{P}$ -labeled cDNA probes using techniques well known in the art (see, for example, Ausubel, *supra*). Labeled probes for Northern analysis may also be produced using commercially available kits (Prime-It Kit, Stratagene, La Jolla, CA). Northern analysis of total RNA obtained from a clinical sample may be performed using classically described techniques. For example, total RNA samples are denatured with formaldehyde / formamide and run for two hours in a 1% agarose, MOPS-acetate-EDTA gel. RNA is then transferred to nitrocellulose membrane by upward capillary action and fixed by UV cross-linkage. Membranes are pre-hybridized for at least 90 minutes and hybridized overnight at 42° C. Post hybridization washes are performed as known in the art (Ausubel, *supra*). The membrane is then exposed to x-ray film overnight with an intensifying screen at -80° C. Labeled membranes are then visualized after exposure to film. The signal produced on the x-ray film by the radiolabeled cDNA probes can then be quantified using any technique known in the art, such as scanning the film and quantifying the relative pixel intensity using a computer program such as NIH Image (National Institutes of Health, Bethesda, MD), wherein the detection of hybridization of a marker-specific probe to the clinical sample is indicative of the presence of the marker sequences and thus may be used to detect cancer such as colon cancer.

In an alternative embodiment, the presence and optionally the quantity of the marker sequences in a clinical sample may be determined using the Taqman™ (Perkin-Elmer, Foster City, CA) technique, which is performed with a transcript-specific antisense probe (i.e., a probe capable of specifically hybridizing to a marker sequence). This probe is specific for a marker sequence PCR product and is prepared with a quencher and fluorescent reporter probe complexed to the 5' end of the oligonucleotide. Different fluorescent markers can be attached to different reporters, allowing for measurement of two products in one reaction (e.g., measurement of the marker sequence). When Taq DNA polymerase is activated, it cleaves off the fluorescent

reporters by its 5'-to-3' nucleolytic activity. The reporters, now free of the quenchers, fluoresce. The color change is proportional to the amount of each specific product and is measured by fluorometer; therefore, the amount of each color can be measured and the RT-PCR product can be quantified. The PCR reactions can be performed in 96 well plates so that samples derived from many individuals can be processed and measured simultaneously. The Taqman™ system has the additional advantage of not requiring gel electrophoresis and allows for quantification when used with a standard curve.

The marker sequence-specific antibodies described above may be used to detect the presence of one or more marker sequences in a biological sample by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitation reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e. g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e. g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e. g., 1-4 hours) at 4 C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4 C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. In the case of immunonprecipitation of a serum sample, however the above protocol is carried out absent the cell lysis step. The ability of the antibody to immunoprecipitate Reg1 $\alpha$  or TIMP1 (or other colon cancer marker) antigen can be assessed by, e. g., western blot analysis. The parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e. g., preclearing the cell lysate with sepharose beads) are well known to those of skill in the art (Ausubel et al, *supra*).

The individual and/or the combinations of the marker sequences may be detected in a biological sample obtained from a patient using Western blot analysis. Briefly, Western blot analysis comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e. g., 8%-20% SDS-PAGE), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e. g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e. g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e. g., an antihuman antibody) conjugated to an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e. g.,  $^{32}\text{P}$  or  $^{125}\text{I}$ ) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. Methods for the optimization of such an analysis are well known in the art (Ausubel, et al., *supra*).

Alternatively, the presence of one or more cancer specific marker sequences in a clinical sample may be detected by ELISA. ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate (or other suitable container) with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest, that is, the antibody which will bind to a cancer-specific marker) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. This method may be modified or optimized according techniques which are known to those of skill in the art.

The binding affinity of an antibody to an antigen and the off-rate of an antibody/antigen interaction can be determined by competitive binding assays. One example of such an assay is a radioimmunoassay comprising the incubation of labeled antigen (e. g., marker labeled with  $^3\text{H}$  or  $^{125}\text{I}$ ) with an anti-marker antibody in the presence of increasing amounts of unlabeled antigen,

and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e. g.,  $^3\text{H}$  or  $^{125}\text{I}$ ) in the presence of increasing amounts of an unlabeled second antibody.

Preferably, the above detection assays may be carried out using antibodies to detect the protein product encoded by a nucleic acid having the sequence of SEQ ID NOs:1-93, or a sequence complementary thereto. In addition, the above detection assays may be conducted using one or more antibodies which specifically recognize and bind to at least one cancer-specific marker. Accordingly, in one embodiment, the assay would include contacting the proteins of the test cell with an antibody specific for the gene product of a nucleic acid represented by SEQ ID NO:1-93, or a sequence complementary thereto, and determining the approximate amount of immunocomplex formation by the antibody and the proteins of the test cell, wherein a detection of such an immunocomplex is indicative of the presence of the antigen, and thus, permits the detection of colon cancer.

Immunoassays, useful in the present invention include those described above, and can also include both homogeneous and heterogeneous procedures such as fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), and nephelometric inhibition immunoassay (NIA).

In another embodiment, the level of the encoded polypeptide product, i.e., the polypeptide product encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:1-93, or a sequence complementary thereto, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker nucleic acid sequence in cells of that patient. Such a method would include the steps of obtaining a sample of a biological sample from the patient, contacting the sample (or proteins from the sample) with an antibody specific for an encoded marker polypeptide, and determining the amount of immune complex formation by the antibody, with the amount of immune complex formation being indicative of the level of the marker encoded polypeptide product in the sample. This determination is particularly instructive when compared to the amount of immune complex

formation by the same antibody in a control sample taken from a normal individual or in one or more samples previously or subsequently obtained from the same person.

In another embodiment, the method can be used to determine the amount of marker polypeptide present in a cell, which in turn can be correlated with progression of a

5 hyperproliferative disorder, e.g., colon cancer. The level of the marker polypeptide can be used predictably to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, transformed cells. Moreover, the subject method can be used to assess the phenotype of cells which are known to be transformed, the phenotyping results being useful in planning a particular therapeutic regimen. For instance, very high levels of the marker  
10 polypeptide in sample cells is a powerful diagnostic and prognostic marker for a cancer, such as colon cancer. The observation of marker polypeptide level can be utilized in decisions regarding, e.g., the use of more aggressive therapies.

#### X Diagnostic assays

The determination of a detectable increase or decrease in the expression level of one or  
15 more marker sequences in a cancer patient compared to a normal patient provides a means of diagnosing or monitoring the patient's disease status, and/or patient response or benefit to cancer therapy. The present invention provides methods for detecting cancer, or alternatively, determining whether a subject is at risk for developing cancer by detecting the disclosed cancer-specific markers (i.e., the nucleic acid sequences of one or more nucleic acid sequences encoding  
20 the cancer specific marker and/or polypeptide sequences of one or more cancer specific markers) for the disease or condition encoded thereby. Examples of cancer include but not limited to, adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, and leukemia. More particularly, examples of cancer also include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non-Hodgkin's lymphoma, pancreatic cancer,  
25 glioblastoma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and various types of head and neck cancer. Preferably, the cancers include  
30 breast, colon, and lung cancer. In a more preferred embodiment, the cancer is colon cancer, and

the marker sequences are the ones comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs:1-93.

5 In clinical applications, human tissue samples can be screened for the presence and/or absence of the biomarkers identified herein. Such samples may comprise tissue samples, whole cells, cell lysates, or isolated nucleic acids, including, for example, needle biopsy cores, surgical resection samples, lymph node tissue, plasma, or serum. For example, these methods include obtaining a biopsy, which is optionally fractionated by cryostat sectioning to enrich tumor cells to about 80% of the total cell population. In certain embodiments, nucleic acids extracted from these samples may be amplified using techniques well known in the art. The levels of selected  
10 markers detected would be compared with statistically valid groups of metastatic, non-metastatic malignant, benign, or normal colon tissue samples.

In one embodiment, the diagnostic method comprises determining whether a subject has an abnormal mRNA or cDNA and/or protein level of the marker sequences. The method comprises using a nucleic acid probe to determine the expression level of the individual and/or  
15 the combinations of the marker sequences in a biological sample obtained from a patient. Specifically, the method comprises:

1. Providing a nucleic acid probe comprising a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably  
20 at least about 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence represented by SEQ ID NOs:1-93, or a sequence complementary thereto;
2. Obtaining a clinical sample from a patient potentially comprising one or more  
25 nucleic acid marker sequences;
3. Providing a second clinical sample from an individual known to not have colon cancer;



4. Contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second clinical samples (e.g., in a Northern blot or *in situ* hybridization assay); and
5. Comparing (a) the amount of hybridization of the probe with RNA of the first clinical sample, with (b) the amount of hybridization of the probe with RNA of the second clinical sample; wherein a statistically difference (e.g., by at least 0.5 fold, at least 2 fold, at least 5 fold, at least 20 fold, or at least 50 fold) in the amount of hybridization with the RNA of the first clinical sample as compared to the amount of hybridization with the RNA of the second clinical sample is indicative of the presence of one or more marker sequences in the first clinical sample.

In one embodiment, the method comprises *in situ* hybridization with a probe derived from a given marker nucleic acid sequence, which nucleic acid sequence is represented by SEQ ID NO:1-93, or a sequence complementary thereto. The method comprises contacting the labeled hybridization probe with a sample of a given type of tissue potentially containing cancerous or pre-cancerous cells as well as normal cells, and determining whether the probe labels some cells of the given tissue type to a degree significantly different (e.g., by at least 0.5 fold, at least 2 fold, at least 5 fold, at least 20 fold, or at least 50 fold) than the degree to which it labels other cells of the same tissue type.

Determining by hybridization whether the target is differentially expressed (e.g., up-regulated or down-regulated) in the sample can also be accomplished by any effective means. For instance, the target's expression pattern in the sample can be compared to its pattern in a known control, such as in a normal tissue, or it can be compared to another target in the same sample. When a second sample is utilized for the comparison, it can be a sample of normal tissue that is known not to contain diseased cells. The comparison can be performed on samples which contain the same amount of RNA (such as polyadenylated RNA or total RNA), or, on RNA extracted from the same amounts of starting tissue. Such a second sample can also be referred to as a control or standard. Hybridization can also be compared to a second target in the same tissue sample. Experiments can be performed that determine a ratio between the target nucleic acid and a second nucleic acid (a standard or control), e.g., in a normal tissue. When the ratio between the target and control are substantially the same in a normal sample, the sample is

determined or diagnosed not to contain cancer cells. However, if the ratio is at least 2 fold different between the normal and sample tissues, the sample is determined to contain cancer cells. The approaches can be combined, and one or more second samples, or second targets can be used. Any second target nucleic acid can be used as a comparison, including "housekeeping" genes, such as beta-actin, alcohol dehydrogenase, or any other gene whose expression does not vary depending upon the disease status of the cell.

Alternatively, the above diagnostic assays may be carried out using antibodies to detect the polypeptides encoded by the nucleic acid marker sequences, which nucleic acid sequences are represented by SEQ ID NOs:1-93, or a sequence complementary thereto. Preferably, the polypeptides have the sequence of one or more of SEQ ID NOs: 94-186. Accordingly, in one embodiment, the assay would include contacting the polypeptides of the test cell or tissue with one or more antibodies specific for the polypeptides represented by SEQ ID NOs: 94-186, and determining the approximate amount of immunocomplex formation by the antibodies and polypeptides of the test cell or tissue, wherein a statistically significant difference in the amount of the immunocomplex formed with the polypeptides of a test or tissue as compared to a normal cell or tissue is an indication that the test cell is cancerous or pre-cancerous. The term "significant difference" refers to a cell phenotype wherein the cell possesses a changed cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin. For example, a cell may have either more or less than about 50%, 25%, 10%, or 5% of the marker polypeptide that a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell and/or a transformed cell of known phenotype.

In one embodiment, the assay is performed as a dot blot assay. The dot blot assay finds particular application where tissue samples are employed as it allows determination of the average amount of the marker polypeptide associated with a single cell by correlating the amount of marker polypeptide in a cell-free extract produced from a predetermined number of cells.

It is well established in the cancer literature that tumor cells of the same type (e.g., breast and/or colon tumor cells) may not show uniformly increased expression of individual oncogenes or uniformly decreased expression of individual tumor suppressor genes. There may also be varying levels of expression of a given marker sequence even between cells of a given type of cancer, further emphasizing the need for reliance on a battery of tests rather than a single test.

Accordingly, in one aspect, the invention provides for a battery of tests utilizing a number of probes of the invention, in order to improve the reliability and/or accuracy of the diagnostic test.

## XI Arrays

In one aspect, the present invention also provides a method wherein nucleic acid probes  
5 are immobilized on a DNA chip in an organized array. Oligonucleotides can be bound to a solid support by a variety of processes, including lithography. These nucleic acid probes comprise a nucleotide sequence at least about 8 nucleotides in length, preferably at least about 12 preferably at least about 15 nucleotides, more preferably at least about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of a sequence which is complementary to  
10 a portion of the coding sequence of a marker nucleic acid sequence represented by SEQ ID NO:1-93 and is differentially expressed in cancer cells, such as colon cancer cells. In some embodiments, the microarrays comprise at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, or more nucleic acids that are complimentary to at least a portion of the coding sequences of the marker sequences comprising a nucleic acid sequence selected from the group consisting of SEQ  
15 ID NOs: 1-93. The present invention provides significant advantages over the available tests for various cancers, such as colon cancer, because it increases the reliability of the test by providing an array of nucleic acid markers on a single chip.

The method includes obtaining a biopsy, which is optionally fractionated by cryostat sectioning to enrich tumor cells to about 80% of the total cell population. The DNA or RNA is  
20 then extracted, amplified, and analyzed with a DNA chip to determine the presence or absence of the marker nucleic acid sequences.

In one embodiment, the nucleic acid probes are spotted onto a substrate in a two-dimensional matrix or array. Samples of nucleic acids can be labeled and then hybridized to the probes. Double-stranded nucleic acids, comprising the labeled sample nucleic acids bound to  
25 probe nucleic acids, can be detected once the unbound portion of the sample is washed away.

The probe nucleic acids can be spotted on substrates including glass, nitrocellulose, etc. The probes can be bound to the substrate by either covalent bonds or by non-specific interactions, such as hydrophobic interactions. The sample nucleic acids can be labeled using radioactive labels, fluorophores, chromophores, etc.

Techniques for constructing arrays and methods of using these arrays are described in EP No. 0 799 897; PCT No. WO 97/292 12; PCT No. WO 97127317; EP No. 0 785 280; PCT No. WO 97/02357; U.S. Pat. No. 5,593,839; U.S. Pat. No. 5,578,832; EP No. 0 728 520; U.S. Pat. No. 5,599,695; EP No. 0 721 016; U.S. Pat. No. 5,556,752; PCT No. WO 95/22058; and U.S. Pat. No. 5,631,734.

In another aspect, the present invention also provides a protein microarrays. Protein microarray technology, which is also known by other names including: protein chip technology and solid-phase protein array technology, is well known to those of ordinary skill in the art and is based on, but not limited to, obtaining an array of identified peptides or proteins on a fixed substrate, binding target molecules or biological constituents to the peptides, and evaluating such binding. See, e.g., G. MacBeath and S. L. Schreiber, "Printing Proteins as Microarrays for High-Throughput Function Determination," *Science* 289(5485):1760-1763, 2000. In general, the protein microarrays include antigen-binding ligands such as antibodies or fragments thereof, fixed to a solid substrate, wherein the ligands specifically bind to the polypeptides encoded by the marker sequences of the present invention. In one embodiment, the protein microarrays further include at least one control polypeptide molecule. In some embodiments, the microarray comprises antibodies or antigen-binding fragments thereof, that bind specifically to least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 different polypeptides encoded by nucleic acid molecules comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1-93. In certain embodiment, the antibodies are monoclonal or polyclonal antibodies. In another certain embodiment, the antibodies are chimeric, human, or humanized antibodies. In yet another certain embodiment, the antibodies are single chain antibodies, and the antigen-binding fragments are F(ab')<sub>2</sub>, Fab, Fd, or Fv fragments.

The solid microarray substrate may include, but not limited to, glass, silica, aluminosilicates, borosilicates, metal oxides such as alumina and nickel oxide, various clays, nitrocellulose, or nylon. The microarray substrates may be coated with a compound to enhance synthesis of a probe (peptide or nucleic acid) on the substrate. Coupling agents or groups on the substrate can be used to covalently link the first nucleotide or amino acid to the substrate. A variety of coupling agents or groups are known to those of skill in the art. Peptide or nucleic acid probes thus can be synthesized directly on the substrate in a predetermined grid.

Alternatively, peptide or nucleic acid probes can be spotted on the substrate, and in such cases the substrate may be coated with a compound to enhance binding of the probe to the substrate.

In these embodiments, presynthesized probes are applied to the substrate in a precise,

predetermined volume and grid pattern, preferably utilizing a computer- controlled robot to

5 apply probe to the substrate in a contact-printing manner or in a non-contact manner such as ink jet or piezo-electric delivery. Probes may be covalently linked to the substrate.

## XII Prognosis, staging, and monitoring of cancer

In one aspect, the present invention provides methods for determining cancer prognosis and stage based on examining the expression levels of the nucleic acid marker sequences and  
10 polypeptides using the methods described in the present invention. If cancer is detected in a subject using a technique other than by determining the expression levels of the marker sequences, then the differential expression level of the marker sequences can be used to determine the prognosis and stage for the subject. As used herein, prognosis refers to the prediction of the probable course and outcome of a disease.

15 In general, methods used for prognosis or stage of cancer involve comparison of the amount of the marker sequences in a sample of interest with that of a control to detect relative differences in the expression of the marker sequences, wherein the difference can be measured qualitatively and/or quantitatively. For example, the expression levels of one or more marker RNAs or polypeptides can be compared with the expression levels of the same marker RNAs or  
20 polypeptides in cancer free or normal samples. Alternatively, the expression levels of one or more marker RNAs or polypeptides can also be compared with the expression levels of the same marker RNAs or polypeptides observed in cancers that are known not to progress. In addition, the expression levels of one or more marker RNAs or polypeptides can also be compared with the expression levels of the same marker RNAs or polypeptides observed in cancers that are  
25 known to progress and/or metastasize.

Also, as used herein, cancer stage refers to the sequence of the events, in which cancer develops and causes symptoms. In addition, staging is a process used to describe how advanced the cancerous state is in patient. Staging systems vary with the types of cancer, but generally involve the following "TNM" system: the type of tumor, indicated by T; whether the cancer has  
30 metastasized to nearby lymph nodes, indicated by N; and whether the cancer has metastasized to

more distant parts of the body, indicated by M. Generally, if a cancer is only detectable in the area of the primary lesion without having spread to any lymph nodes it is called Stage I. If it has spread only to the closest lymph nodes, it is called Stage II. In Stage III, the cancer has generally spread to the lymph nodes in near proximity to the site of the primary lesion. Cancers that have spread to a distant part of the body, such as the liver, bone, brain or other site, are Stage IV, the most advanced stage. Methods of the present invention are useful in assaying the staging of cancer. The staging of cancer can be accomplished by determining the expression levels of one or more marker RNAs or polypeptides to a reference expression levels of the same marker RNAs or polypeptides. The reference expression levels of the marker RNAs or polypeptides can be that from cancer free or healthy or cancer samples, wherein the cancer can be at different stages in development.

The present invention further provides methods of monitoring cancer progression or recurrence by measuring the expression levels of the marker RNAs or polypeptides over the time. In one embodiment, the methods comprise:

- (1). detecting in a biological sample of the subject at a first point in time, the expression of one or more nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93;
- (2). repeating step (a) at a subsequent point in time; and
- (3). comparing the expression level detected in steps (a) and (b), wherein a change in the expression level is indicative of progression of cancer or a pre-malignant condition thereof in the subject.

In another embodiment, the methods comprise:

- (1). detecting in a biological sample of the subject at a first point in time, the expression of one or more polypeptides comprising one or more polypeptide sequences selected from the group consisting of SEQ ID NOs: 94-186;
- (2). repeating step (a) at a subsequent point in time; and

(3). comparing the expression level detected in steps (a) and (b), wherein a change in the expression level is indicative of progression of cancer or a pre-malignant condition thereof in the subject.

For example, elevated expression levels of one or more over-expressed marker RNAs or polypeptides, or reduced expression levels of one or more under-expressed marker RNAs or polypeptides in a subsequent point in time relative to an earlier point in time, indicate that the cancer is progressing to a more severe stage. On the other hand, reduced expression levels of one or more over-expressed marker RNAs or polypeptides, or elevated expression levels of one or more under-expressed marker RNAs or polypeptides in a subsequent point in time relative to an earlier point in time, indicate that the cancer is not progressing or is progressing slowly.

The methods used in prognosis, staging, and monitoring cancer can be applied to various types of cancer. Examples of cancer include but not limited to, adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, and leukemia. More particularly, examples of cancer also include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non-Hodgkin's lymphoma, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer such as hepatic carcinoma and hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, salivary gland carcinoma, kidney cancer such as renal cell carcinoma and Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, esophageal cancer, and various types of head and neck cancer. Preferably, the cancers include breast, colon, and lung cancer. More preferably, the cancer is colon cancer, and the marker sequences are the ones comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-93.

### XIII Efficacy of therapy and therapeutic compositions

In one aspect, the present invention also provides methods that permit the assessment and/or monitoring of patients who will be likely to benefit from both traditional and non-traditional treatments and therapies for cancers, particularly colon cancer. The present invention thus embraces testing, screening and monitoring of patients undergoing anti-cancer treatments and therapies, used alone, in combination with each other, and/or in combination with anti-cancer drugs, anti-neoplastic agents, chemotherapeutics and/or radiation and/or surgery, to treat cancer patients.

An advantage of the present invention is the ability to monitor, or screen over time, those patients who can benefit from one, or several, of the available cancer therapies, and preferably, to monitor patients receiving a particular type of therapy, or a combination therapy, over time to determine how the patient is faring from the treatment(s), if a change, alteration, or cessation of treatment is warranted; if the patient's disease has been reduced, ameliorated, or lessened; or if the patient's disease state or stage has progressed, or become metastatic or invasive. The cancer treatments embraced herein also include surgeries to remove or reduce in size a tumor, or tumor burden, in a patient. Accordingly, the methods of the invention are useful to monitor patient progress and disease status post-surgery.

The identification of the correct patients for a cancer therapy according to this invention can provide an increase in the efficacy of the treatment and can avoid subjecting a patient to unwanted and life-threatening side effects of the therapy. By the same token, the ability to monitor a patient undergoing a course of therapy using the methods of the present invention can determine whether a patient is adequately responding to therapy over time, to determine if dosage or amount or mode of delivery should be altered or adjusted, and to ascertain if a patient is improving during therapy, or is regressing or is entering a more severe or advanced stage of disease, including invasion or metastasis, as discussed further herein.

A method of monitoring according to this invention reflects the serial, or sequential, testing or analysis of a cancer patient by testing or analyzing the patient's body fluid sample over a period of time, such as during the course of treatment or therapy, or during the course of the patient's disease. For instance, in serial testing, the same patient provides a body fluid sample, e.g., serum or plasma, or has sample taken, for the purpose of observing, checking, or examining the expression levels of one or more of the markers (RNA or polypeptide) of the invention in the patient by measuring the levels of one or more of these markers during the course of treatment, and/or during the course of the disease, according to the methods of the invention.

Similarly, a patient can be screened over time to assess the levels of one or more of the markers in a biological sample for the purposes of determining the status of his or her disease and/or the efficacy, reaction, and response to cancer or neoplastic disease treatments or therapies that he or she is undergoing. It will be appreciated that one or more pretreatment sample(s) is/are optimally taken from a patient prior to a course of treatment or therapy, or at the start of the treatment or therapy, to assist in the analysis and evaluation of patient progress and/or response



at one or more later points in time during the period that the patient is receiving treatment and undergoing clinical and medical evaluation.

In monitoring a patient's levels of one or more of the markers of the invention over a period of time, which may be days, weeks, months, and in some cases, years, or various intervals thereof, the patient's body fluid sample, e.g., a serum or plasma sample, is collected at intervals, as determined by the practitioner, such as a physician or clinician, to determine the levels of one or more of the markers in the cancer patient compared to the respective levels of one or more of these analytes in normal individuals over the course or treatment or disease. For example, patient samples can be taken and monitored every month, every two months, or combinations of one, two, or three month intervals according to the invention. Quarterly, or more frequent monitoring of patient samples, is advisable.

The levels of the one or more markers found in the patient are compared with the respective levels of the one or more of these markers in normal individuals, and with the patient's own marker levels, for example, obtained from prior testing periods, to determine treatment or disease progress or outcome. Accordingly, use of the patient's own marker levels monitored over time can provide, for comparison purposes, the patient's own values as an internal personal control for long-term monitoring of marker levels, and thus cancer presence and/or progression. As described herein, following a course of treatment or disease, the determination of an increase or a decrease in one or more of the marker levels in the cancer patient over time compared to the respective levels of one or more of these markers in normal individuals reflects the ability to determine the severity or stage of a patient's cancer, or the progress, or lack thereof, in the course or outcome of a patient's cancer therapy or treatment.

Increases or decreases in the levels of the markers in cancer patients are determined by comparing the values obtained from analyzing cancer patient samples compared to the normal control range expression levels. A biomarker is said to be over-expressed if expression of the marker is at least 2 fold greater in the cancer patient relative to a normal control, and a biomarker is said to be under expressed if the expression of the marker is at least 2 fold greater in the normal control relative to in the cancer patient.

In monitoring a patient over time, a reduction in the levels of one or more of a patient's marker levels from increased levels (i.e., at least 2 fold over-expressed) compared to normal

range values to levels at or near to the levels of the analytes found in normal individuals is indicative of treatment progress or efficacy, and/or disease improvement, remission, tumor reduction or elimination, and the like. Likewise, in all of the methods described in the embodiments of this invention, a determination of a reduction of one or more of a patient's marker levels from an elevated level (i.e., at least 2 fold over-expressed) to, or approximately to, the respective levels of one or more of these analytes found in normal individuals provides a further aspect of the methods of the invention, in which a patient's improvement, recovery or remission, and/or treatment progress or efficacy, is able to be ascertained over time following performance of the method.

Another embodiment of the present invention encompasses a method of monitoring a cancer patient's course of disease, or the efficacy of a cancer patient's treatment or therapy. The patient's treatment or therapy can involve traditional therapies, such as hormone therapy, chemotherapeutic drug therapy, radiation, or novel therapies, or a combination of any of the foregoing. The method involves measuring levels of one or more markers in a body fluid sample of the cancer patient and determining if the levels of one or more of the markers in the patient's sample are changed by at least 2 fold compared to the respective levels of one or more of these analytes in normal controls during the course of disease or cancer treatment. In accordance with the method, a change in the levels of the marker in the cancer patient compared to the respective levels of the marker in normal controls is indicative of a change in stage, grade, severity or progression of the patient's cancer and/or a lack of efficacy or benefit of the cancer treatment or therapy provided to the patient during a course of treatment, e.g., poor treatment or clinical outcome.

As will be understood by the skilled practitioner in the art, the monitoring method according to this invention is preferably, performed in a serial or sequential fashion, using samples taken from a patient during the course of disease, or a disease treatment regimen, (e.g., after a number of days, weeks, months, or occasionally, years, or various multiples of these intervals) to allow a determination of disease progression or outcome, and/or treatment efficacy or outcome. If the sample is amenable to freezing or cold storage, the samples may be taken from a patient (or normal individual) and stored for a period of time prior to analysis.

In another of its embodiments, the present invention encompasses the determination of the amounts or levels of one or more additional cancer markers in conjunction with the

determination of the levels of one or more of the markers of the invention in a sample to be analyzed.

The present invention also includes a method of assessing the efficacy of a test composition for inhibiting cancers, such as colon cancer. As described above, differential expression levels of the marker sequences of the invention correlate with the cancerous state of cancer cells, particularly colon cancer cells. It is recognized that changes in the expression levels of the marker sequences of the present invention result from the cancerous state of cells. Thus, composition which inhibit cancer in a patient will cause the expression levels of the marker sequences to change to a level near the normal level of expression for the marker sequences. The method thus comprises comparing expression levels of one or more marker sequences in a first biological sample maintained in the presence of a test composition with those of the same marker sequences in a second biological sample maintained in the absence of the test composition. A significant difference in the expression levels of one or more marker sequences is an indication that the test composition inhibits the cancer. In a preferred embodiment, the cancer is colon cancer, and the marker sequences are the ones listed in Tables 1 and 2. In another embodiment, the cell samples may be aliquots of a single sample obtained from either a healthy subject or a patient with cancerous conditions.

#### XIV Modulators of the marker sequences

It is recognized that changes in the expression levels of the marker sequences likely induce, maintain, and promote the cancerous state of cells. Thus, another aspect of the present invention is directed to the modulators of the marker sequences capable of modulating the differentiation and proliferation of cells. In this regard, the present invention provides assays for determining compounds that modulate the expression of the marker sequences. The compounds can be used to modulate the biological activity of the polypeptides encoded by the marker sequences or the marker sequences themselves. Compounds can also be useful in a variety of different environments, including as medicinal agents to treat or prevent disorders associated with cancer.

Methods of identifying compounds generally comprise steps in which a compound is placed in contact with a marker sequence, its transcription product, its translation product, or other target, and determination of whether the compound modulates the marker sequence. For

modulating the expression of a marker sequence, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting the marker sequence (e.g., in a cell population) with a test compound under conditions effective for said test compound to modulate the expression of the marker sequence, and determining whether said test agent modulates said sequence. A compound can modulate expression of a sequence at any level, including transcription (e.g., by modulating the promoter), translation, and/or perdurance of the nucleic acid (e.g., degradation, stability, etc.) in the cell.

For modulating the biological activity of polypeptides, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a polypeptide (e.g., in a cell, lysate, or isolated) with a test compound under conditions effective for said test agent to modulate the biological activity of said polypeptide, and determining whether said test compound modulates said biological activity.

Contacting the polynucleotide or polypeptide with the test compound can be accomplished by any suitable method and/or means that places the compound in a position to functionally control expression or biological activity of the gene or its product in the sample. Functional control indicates that the compound can exert its physiological effect through whatever mechanism it works. The choice of the method and/or means can depend upon the nature of the compound and the condition and type of environment in which the gene or its product is presented, e.g., lysate, isolated, or in a cell population (such as, *in vivo*, *in vitro*, organ explants, etc.). For example, if the cell population is an *in vitro* cell culture, the compound can be contacted with the cells by adding it directly into the culture medium. If the compound cannot dissolve readily in an aqueous medium, it can be incorporated into liposomes, or another lipophilic carrier, and then administered to the cell culture. Contact can also be facilitated by incorporation of compound with carriers and delivery molecules and complexes, by injection, by infusion, etc.

After the agent has been administered in such a way that it can gain access to the gene or gene product (including DNA, mRNA, and polypeptides), it can be determined whether the test compound modulates its expression or biological activity. Modulation can be of any type, quality, or quantity, e.g., increase, facilitate, enhance, up-regulate, stimulate, activate, amplify, augment, induce, decrease, down-regulate, diminish, lessen, reduce, etc. The modulatory quantity can also encompass any value, e.g., 1%, 5%, 10%, 50%, 75%, 1-fold, 2-fold, 5-fold, 10-

fold, 100-fold, etc. To modulate gene expression means, e.g., that the test compound has an effect on its expression, e.g., to effect the amount of transcription, to effect RNA splicing, to effect translation of the RNA into polypeptide, to effect RNA or polypeptide stability, to effect polyadenylation or other processing of the RNA, to effect post-transcriptional or post-translational processing, etc. To modulate biological activity means, e.g., that a functional activity of the polypeptide is changed in comparison to its normal activity in the absence of the compound. This effect includes, increase, decrease, block, inhibit, enhance, etc.

A test compound can be of any molecular composition, e.g., chemical compounds, biomolecules, such as polypeptides, lipids, nucleic acids (e.g., antisense to a polynucleotide) carbohydrates, antibodies, ribozymes, double-stranded RNA, aptamers, etc. For example, if a polypeptide to be modulated is a cell-surface molecule, a test compound can be an antibody that specifically recognizes it and, e.g., causes the polypeptide to be internalized, leading to its down-regulation on the surface of the cell. Such effect does not have to be permanent, but can require the presence of the antibody to continue the down-regulatory effect. Antibodies can also be used to modulate the biological activity of a polypeptide in a lysate or other cell-free form.

#### XV Drug screening

In one aspect, the present invention is also directed to methods for screening drugs that inhibit cancer, particularly colon cancer. Drug screening is performed by adding a test compound to a sample of cells, and monitoring the effect. A parallel sample which does not receive the test compound is also monitored as a control. The treated and untreated cells are then compared by any suitable phenotypic criteria, including but not limited to microscopic analysis, viability testing, ability to replicate, histological examination, the level of a particular RNA or polypeptide associated with the cells, the level of enzymatic activity expressed by the cells or cell lysates, and the ability of the cells to interact with other cells or compounds. Differences between treated and untreated cells indicates effects attributable to the test compound.

Desirable effects of a test compound include an effect on any phenotype that was conferred by the cancer-associated marker nucleic acid sequence. Examples include a test compound that limits the overabundance of mRNA, limits production of the encoded protein, or limits the functional effect of the protein. The effect of the test compound would be apparent when comparing results between treated and untreated cells. For example, candidate compounds

may be identified that down-regulate expression of one specific gene. In one embodiment, candidate compounds may be identified that up-regulate expression of one specific gene. Generally a plurality of assay mixtures are run in parallel with different compound concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection.

Screening assays can be based upon any of a variety of techniques readily available and known to one of ordinary skill in the art. In general, the screening assays involve contacting a cancerous cell (preferably a cancerous colon cell) with a candidate agent, and assessing the effect upon biological activity of a differentially expressed gene product. The effect upon a biological activity can be detected by, for example, detection of expression of a gene product of a differentially expressed gene (e.g., a decrease in mRNA or polypeptide levels, would in turn cause a decrease in biological activity of the gene product). Alternatively or in addition, the effect of the candidate agent can be assessed by examining the effect of the candidate agent in a functional assay. For example, where the differentially expressed gene product is an enzyme, then the effect upon biological activity can be assessed by detecting a level of enzymatic activity associated with the differentially expressed gene product. The functional assay will be selected according to the differentially expressed gene product.

The screening methods may include both *in vitro* and *in vivo* screening of a cell or tissue. One particular embodiment of *in vitro* method comprises a method of determining the efficacy of a test compound for inhibiting cancer in a subject, the method comprising comparing a) the expression level of one or more nucleic acid sequences in a first biological sample from the subject wherein the sample has been exposed to the test compound, with b) the expression level of said nucleic acid sequences in a second biological sample from the subject wherein the sample has not been exposed to the test compound, said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93, wherein a change of at least two fold in the expression level of said nucleic acid sequences is an indication that the test compound is efficacious for inhibiting cancer in the subject.

In another embodiment, the *in vivo* methods of screening for compounds that alter the expression of the marker sequences comprise exposing a subject, preferably a mammal having cancer cells in which the marker sequences (either at mRNA or polypeptide level) are detectable,

to a compound, and determining the level of the marker sequences. Where the differentially expressed gene is increased in expression in a cancerous cell, the compound of interest is those that decrease activity of the differentially expressed gene product, and where the differentially expressed gene is decreased in expression in a cancerous cell, the compound of interest is those that increase activity of the differentially expressed gene product.

Assays for determining the differentially expressed marker sequences (described *supra*) can be readily adapted in the screening assay embodiments of the present invention. Exemplary assays useful in screening candidate compounds include, but are not limited to, hybridization-based assays (e.g. use of nucleic acid probes or primers to assess expression levels), antibody-based assays (e.g. to assess levels of polypeptide gene products), binding assays (e.g. to detect interaction of a candidate agent with a differentially expressed polypeptide, which assays may be competitive assays where a natural or synthetic ligand for the polypeptide is available), and the like. Additional exemplary assays include, but are not necessarily limited to, cell proliferation assays, antisense knockout assays, assays to detect inhibition of cell cycle, assays of induction of cell death/apoptosis, and the like.

In one embodiment, the candidate compound is naturally occurring or modified proteins. In another embodiment, candidate compounds are peptides. The peptides may be digests of naturally occurring proteins, or the one made by chemical synthesis. Furthermore, the synthetic process can be designed to generate randomized proteins, to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized candidate proteinaceous drugs.

In another embodiment, the candidate compounds are nucleic acids, either naturally occurring or modified. In a preferred embodiment, the nucleic acid compounds are antisense nucleic acids. Drug candidates that are antisense molecules include antisense or sense oligonucleotides comprising a single-strand nucleic acid sequence (either RNA or DNA) capable of binding to target mRNA or DNA sequences for lung cancer molecules identified by the methods of the invention.

In yet another preferred embodiment, drug candidates are antibodies. An antibody used in methods for screening for a candidate drug may either bind a full length protein or a fragment thereof. In a preferred embodiment, the antibody binds a unique epitope on a target protein and

shows little or no cross-reactivity. The term "antibody" is understood to include antibody fragments, as are known in the art, including Fab, Fab<sub>2</sub>, single chain antibodies (Fv for example), chimeric antibodies, etc., either produced by the modification of whole antibodies or those synthesized de novo using recombinant DNA technologies known in the art. Antibodies as used  
5 herein as drug candidates include both polyclonal and monoclonal antibodies. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an antigenic agent and, if desired, an adjuvant. It may be useful to conjugate the antigenic agent to a protein known to be immunogenic in the mammal being immunized.

In yet another embodiment, the candidate compounds are chemical compounds. In a  
10 preferred embodiment, the candidate compounds are small organic compounds having a molecular weight of more than 100 and less than about 2500 daltons. Candidate compounds may also include functional groups necessary for structural interaction with proteins or nucleic acids.

#### XVI Kits

The present invention also provides for kits that contain the necessary reagents for  
15 detection of the expression levels (either at RNA or polypeptide level) of the individual and/or combinations of marker sequences in a biological sample. Reagents can include marker sequence-specific probes/primers and antibodies as described *supra*. Kits can also contain a control/reference value or a set of control/reference values indicating normal and various clinical progression stages of cancer. In a preferred embodiment, the control/reference value or a set of  
20 control/reference values are indicative of normal and various clinical progression stages of colon cancer. Moreover, kits can contain positive controls, and/or negative controls for comparison with the test sample. A negative control can contain a sample that does not have any marker RNA or polypeptide. A positive control can contain a sample that have various known levels of marker RNA or polypeptide. Kits can also contain any combinations of the marker sequence-  
25 specific probes/primers and/or antibodies. Kits can also contain instructions for conducting the assays and for interpreting the results. For antibody-based kit, the kit can comprise, for example: (1) a first antibody (e.g., attached to a solid support) which binds to a polypeptide corresponding to a marker of the invention; and, optionally, (2) a second, different antibody which binds to either the polypeptide or the first antibody and is conjugated to a detectable label. For  
30 oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, e.g., a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a



polypeptide corresponding to a marker sequence of the invention or (2) a pair of primers useful for amplifying a nucleic acid molecule corresponding to a marker of the invention. The kit can also comprise, e.g., a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (e.g., an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

Such kits can be used to determine whether a subject is suffering from or at an increased risk of developing cancer, particularly colon cancer. Furthermore, such kits can be used to determine the prognosis, stage, or monitoring the progression of cancer, particularly colon cancer. Furthermore, such kits can be used for drug screening or for selection of treatment for cancer, particularly colon cancer.

#### Examples

The examples below are non-limiting and are merely representative of various aspects and features of the present invention.

##### Example 1. Identification of differentially expressed marker sequences

Twenty well characterized, microdissected samples of colorectal cancer tissue were obtained from consenting patients. A second set of twenty, microdissected samples of normal adjacent colon tissue were also obtained. Total RNA was extracted from these samples using RNeasy kits (QIAGEN, Valencia, CA) according to the manufacturer's instructions. Expression profiling was performed using the GeneChip expression arrays from Affymetrix (Santa Clara, CA). Reverse transcription, second-strand synthesis, and probe generation was accomplished by standard Affymetrix protocols. The Human Genome U133A GeneChip, which contains more than 15,000 substantiated human genes, was hybridized, washed, and scanned according to Affymetrix protocols. Changes in cellular mRNA levels in the cancerous tissues were compared with mRNA levels in the normal colon tissues. GeneSpring v4.2 (Silicon Genetics, Redwood City, CA) was used to normalize and scale results and compare gene expression levels in the cancer tissue relative to that in the normal tissue.

Applying a set of filters to the normalized data identified the up- and down-regulated genes. First, a non-parametric test defined the genes that were statistically associated with either the cancer or the normal samples. Next, a pair of filters was used to remove the genes with low signals and to set a high threshold for a minimum expression levels. The final filter required a three-fold average expression difference between the two conditions (cancer and normal).

This analysis resulted in 47 genes that were up-regulated in the colorectal cancer tissue relative to the normal adjacent colon tissue. These genes are identified in Table 1. Likewise, 46 down-regulated genes were identified in the colorectal cancer tissue relative to the normal adjacent colon tissue. These genes are listed in Table 2.

#### Other embodiments

Other embodiments will be evident to those of skill in the art. It should be understood that the foregoing detailed description is provided for clarity only and is merely exemplary. The spirit and scope of the present invention are not limited to the above examples, but are encompassed by the following claims.

**Claims**

1. A method of detecting differential expression of one or more nucleic acid sequences in a biological sample, comprising:

(a) obtaining the sample from a subject; and

5 (b) detecting a change in the expression level of one or more nucleic acid sequences relative to a control expression level of the nucleic acid sequences, said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93.

2. The method of claim 1, wherein said step of detecting comprises:

10 (a) contacting said sample with a polynucleotide probe comprising at least 12 consecutive nucleotides of a nucleic acid sequence, said probe is capable of hybridizing under stringent conditions to a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-93;

(b) detecting the hybridization of said polynucleotide probe to said nucleic acid  
15 sequence selected from the group consisting of SEQ ID NOs: 1-93, wherein the signal intensity of hybridization is indicative of the expression level of a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1-93.

3. The method of claim 2, wherein said probe comprises a detectable label.

4. The method of claim 1, wherein said change in the expression level is either an increase  
20 or an decrease in expression level.

5. The method of claim 1, wherein said change in the expression level is at least two fold.

6. A method of detecting cancer or a pre-malignant condition thereof in a subject comprising comparing a) the expression level of one or more nucleic acid sequences in a biological sample from the subject with b) a control expression level of said nucleic acid  
25 sequences, said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93, wherein a change of at least two-fold in the

expression level of said nucleic acid sequences is indicative of cancer or pre-malignant condition.

7. The method of claim 6, wherein said change in the expression level is either an increase or decrease in the expression level.

5 8. A method of monitoring the onset, progression, or regression of cancer or a pre-malignant condition thereof in a subject, the method comprising:

(a) detecting in a biological sample of the subject at a first point in time, the expression of one or more nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93;

10 (b) repeating step (a) at a subsequent point in time; and

(c) comparing the expression level detected in steps (a) and (b), wherein a change in the expression level is indicative of progression of cancer or a pre-malignant condition thereof in the subject.

15 9. The method of claim 8, wherein the change in the expression level is either an increase or decrease.

10. A method of determining prognosis for cancer or a pre-malignant condition thereof in a subject, comprising:

20 (a) detecting in a biological sample of the subject, the expression level of one or more nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93;

(b) comparing the expression level detected in steps (a) with a reference expression level of said nucleic acid sequences; and

(c) evaluating the prognosis of the subject based on the comparison in step (b).

25 11. The method of claim 10, wherein the reference expression level is the expression level of said nucleic acid sequences in cancer free or normal sample.

12. The method of claim 10, wherein the reference expression level is the expression level of said nucleic acid sequences cancer samples that are known not to progress to aggressive form.

13. A method of determining the efficacy of a test compound for inhibiting cancer in a subject, the method comprising comparing a) the expression level of one or more nucleic acid sequences in a first biological sample from the subject wherein the sample has been exposed to the test compound, with b) the expression level of said nucleic acid sequences in a second biological sample from the subject wherein the sample has not been exposed to the test compound, said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93, wherein a change of at least two fold in the expression level of said nucleic acid sequences is an indication that the test compound is efficacious for inhibiting cancer in the subject.

14. The method of claim 13, wherein the change in the expression level is either an increase or decrease.

15. A method of determining the efficacy of a therapy for inhibiting cancer in a subject, the method comprising comparing a) the expression level of one or more nucleic acid sequences in a first biological sample from the subject prior to providing at least a portion of the therapy to the subject, with b) the expression level of said nucleic acid sequences in a second biological sample from the subject following the provision of the portion of the therapy, said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93, wherein a change of at least two fold in the expression level of said nucleic acid sequences is an indication that the therapy is efficacious for inhibiting cancer in the subject.

16. The method of claim 15, wherein the change in the expression level is either an increase or decrease.

17. A method of selecting a composition for inhibiting cancer in a subject, the method comprising:

- (a) obtaining a first biological sample comprising cancer cells from the subject;
- (b) separately exposing aliquots of the sample in the presence of a plurality of test compositions;

(c) comparing the expression level of one or more nucleic acid sequences in each of the aliquots from (b) with the expression level in the sample produced by (a), said nucleic acid sequences comprising one or more nucleic acid sequences selected from the group consisting of SEQ ID NOs: 1-93; and

5 (d) selecting one of the test compositions which induces a change of at least two fold in the expression level of said nucleic acid sequences in one aliquot containing the test composition.

18. The method of claim 17, wherein the change in the expression level is either an increase or decrease.

10 19. A method of inhibiting cancer in a subject, the method comprising:

(a) obtaining a first biological sample comprising cells from the subject;

(b) administering to the subject one or more test compositions;

(c) obtaining a second biological sample comprising cells from the subject of (b); and

15 (d) comparing the expression level of one or more nucleic acid sequences in the first sample with the expression level of said nucleic acid sequences in the second sample, wherein a change of at least two fold in the expression level is indicative of inhibition of cancer by said test compositions.

20. A polypeptide comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186.

20 21. An antibody that specifically binds to a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186.

22. The antibody of claim 21, wherein said antibody is polyclonal antibody.

23. The antibody of claim 21, wherein said antibody is monoclonal antibody.

24. A method of detecting in a biological sample the presence of a polypeptide comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, said method comprising:

(a) obtaining said biological sample from a subject;

5 (b) contacting said sample with a polypeptide ligand which is capable of binding to one or more of SEQ ID NOs: 94-186; and

(c) detecting the binding of said polypeptide ligand to said polypeptide, wherein detecting of binding is indicative of the presence of said polypeptide sequence comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186 in said  
10 biological sample.

25. The method of claim 24, wherein the polypeptide ligand is an antibody.

26. The method of claim 24, wherein the polypeptide ligand comprises a detectable label.

27. The method of claim 25, wherein the antibody is a monoclonal antibody.

28. A method of detecting cancer or a pre-malignant condition thereof in a subject  
15 comprising:

(a) obtaining a biological sample from a subject;

(b) contacting the sample with one or more polypeptide ligands that bind specifically to one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186;

20 (c) determining specific binding; and

(d) comparing the specific binding between the polypeptide ligands and the polypeptides in the sample with the specific binding between the polypeptide ligands and the polypeptides in a cancer-free sample, wherein a significant change in the specific binding is diagnostic for cancer in the subject.

29. A method of monitoring the onset, progression, or regression of cancer in a subject, comprising:

(a) contacting at a first point in time a first biological sample with one or more polypeptide ligands that specifically bind to one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, determining specific binding between the polypeptide ligands and the polypeptides;

(b) contacting at a subsequent point in time a second biological sample with said polypeptide ligands that specifically bind to one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, determining specific binding between the polypeptide ligands and the polypeptides; and

(c) comparing the specific binding in the first biological sample to the specific binding in the second biological sample, wherein a significant change in the specific binding is an indication of the onset, progression, or regression of cancer.

30. A method of determining prognosis for cancer or a pre-malignant condition thereof in a subject, comprising:

(a) contacting a biological sample obtained from a subject having cancer with one or more polypeptide ligands that bind specifically to one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186;

(b) determining specific binding;

(c) comparing the specific binding between the polypeptide ligands and the polypeptides in the sample with the specific binding between the polypeptide ligands and the polypeptides either in a cancer-free sample or in a cancer sample that is known not to progress to aggressive form; and

(d) evaluating the prognosis of the subject based on the comparison in step (c).

31. A method of determining the efficacy of a test compound for inhibiting cancer in a subject, the method comprising comparing a) in a first biological sample from the subject binding between one or more polypeptide ligands that specifically bind to one or more



polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186 and one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, wherein the sample has not been exposed to the test compound, with b) in a second biological sample from the subject, the specific binding of said polypeptide ligands and said polypeptides, wherein the sample has been exposed to the test compound, and wherein a significant change in the specific binding is an indication that the test compound is efficacious for inhibiting cancer in the subject.

32. A method of determining the efficacy of a therapy for inhibiting cancer in a subject, comprising comparing a) in a first biological sample from the subject prior to a treatment, binding between one or more polypeptide ligands that specifically bind to one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186 and one or more polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, with b) in a second biological sample from the subject following the treatment, the specific binding of said polypeptide ligands and said polypeptides, and wherein a significant change in the specific binding is an indication that the test compound is efficacious for inhibiting cancer in the subject.

33. A method of selecting a composition for inhibiting cancer in a subject, comprising

- (a) obtaining a first biological sample comprising cancer cells from the subject;
- (b) separately exposing aliquots of the sample in the presence of a plurality of test compositions;

(c) comparing the specific binding between one or more polypeptide ligands and one or more polypeptides in each of the aliquots from (b) with the specific binding between said polypeptide ligands and said polypeptides in each of the aliquots from (a), wherein said ligands comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, and wherein said polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186; and

(d) selecting one of the test compositions which induces a significant change in specific binding .

34. A method of inhibiting cancer in a subject with cancer, comprising:

- (a) obtaining a first biological sample comprising cells from the subject;
- (b) administering to the subject one or more test compositions;
- (c) obtaining a second biological sample comprising cells from the subject of (b); and

5 (d) comparing the specific binding between one or more polypeptide ligands and one or more polypeptides in the first sample with the specific binding between said polypeptide ligands and said polypeptides in the second sample, wherein said ligands comprising a polypeptide sequence selected from the group consisting of SEQ ID NOs: 94-186, and wherein said polypeptides comprising a polypeptide sequence selected from the group consisting of SEQ  
10 ID NOs: 94-186, and wherein a significant change in the specific binding is an indication of inhibition cancer by said test compositions.

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 <213> Homo sapiens

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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 <213> Homo sapiens

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## SEQUENCE LISTING 1657-2022.txt

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 <212> DNA  
 <213> Homo sapiens

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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&lt;213&gt; Homo sapiens

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&lt;213&gt; Homo sapiens

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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 <213> Homo sapiens

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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&lt;211&gt; 2090

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 57

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## SEQUENCE LISTING 1657-2022.txt

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&lt;213&gt; Homo sapiens

&lt;400&gt; 70

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## SEQUENCE LISTING 1657-2022.txt

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&lt;211&gt; 1427

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 73

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&lt;211&gt; 2396

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 74

## SEQUENCE LISTING 1657-2022.txt

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&lt;211&gt; 2863

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 75

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## SEQUENCE LISTING 1657-2022.txt

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 <212> DNA  
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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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## SEQUENCE LISTING 1657-2022.txt

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&lt;211&gt; 3311

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 87

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## SEQUENCE LISTING 1657-2022.txt

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 <212> DNA  
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## SEQUENCE LISTING 1657-2022.txt

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&lt;400&gt; 90

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aaaaaaa 367

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&lt;210&gt; 91

&lt;211&gt; 396

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

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&lt;211&gt; 632

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 92

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&lt;210&gt; 93

&lt;211&gt; 257

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 93

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&lt;210&gt; 94

&lt;211&gt; 422

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 94

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35      40      45

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## SEQUENCE LISTING 1657-2022.txt

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 85 90 95  
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 100 105 110  
 Pro Gly Ser Lys Lys Asp Tyr Ser Gln Tyr Glu Glu Asn Ile Thr His  
 115 120 125  
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 Arg Asp Leu Asp Thr Trp Tyr Lys Glu Gln Ser Ala Ala Met Ser Gln  
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 Glu Ala Ala Ser Pro Ala Thr Val Gln Ser Arg Gln Gly Asp Ile His  
 275 280 285  
 Glu Leu Lys Arg Thr Phe Gln Ala Leu Glu Ile Asp Leu Gln Thr Gln  
 290 295 300  
 Tyr Ser Thr Lys Ser Ala Leu Glu Asn Met Leu Ser Glu Thr Gln Ser  
 305 310 315 320  
 Arg Tyr Ser Cys Lys Leu Gln Asp Met Gln Glu Ile Ile Ser His Tyr  
 325 330 335  
 Glu Glu Glu Leu Thr Gln Leu Arg His Glu Leu Glu Arg Gln Asn Asn  
 340 345 350  
 Glu Tyr Gln Val Leu Leu Gly Ile Lys Thr His Leu Glu Lys Glu Ile  
 355 360 365  
 Thr Thr Tyr Arg Arg Leu Leu Glu Gly Glu Ser Glu Gly Thr Arg Glu  
 370 375 380  
 Glu Ser Lys Ser Ser Met Lys Val Ser Ala Thr Pro Lys Ile Lys Ala  
 385 390 395 400  
 Ile Thr Gln Glu Thr Ile Asn Gly Arg Leu Val Leu Cys Gln Val Asn  
 405 410 415  
 Glu Ile Gln Lys His Ala  
 420

&lt;210&gt; 95

&lt;211&gt; 166

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 95

Met Ala Gln Thr Ser Ser Tyr Phe Met Leu Ile Ser Cys Leu Met Phe  
 1 5 10 15  
 Leu Ser Gln Ser Gln Gly Gln Glu Ala Gln Thr Glu Leu Pro Gln Ala  
 20 25 30  
 Arg Ile Ser Cys Pro Glu Gly Thr Asn Ala Tyr Arg Ser Tyr Cys Tyr  
 35 40 45  
 Tyr Phe Asn Glu Asp Arg Glu Thr Trp Val Asp Ala Asp Leu Tyr Cys  
 50 55 60  
 Gln Asn Met Asn Ser Gly Asn Leu Val Ser Val Leu Thr Gln Ala Glu  
 65 70 75 80  
 Gly Ala Phe Val Ala Ser Leu Ile Lys Glu Ser Gly Thr Asp Asp Phe  
 85

## SEQUENCE LISTING 1657-2022.txt

```

      85      90      95
Asn Val Trp Ile Gly Leu His Asp Pro Lys Lys Asn Arg Arg Trp His
      100      105      110
Trp Ser Ser Gly Ser Leu Val Ser Tyr Lys Ser Trp Gly Ile Gly Ala
      115      120      125
Pro Ser Ser Val Asn Pro Gly Tyr Cys Val Ser Leu Thr Ser Ser Thr
      130      135      140
Gly Phe Gln Lys Trp Lys Asp Val Pro Cys Glu Asp Lys Phe Ser Phe
      145      150      155      160
Val Cys Lys Phe Lys Asn
      165

```

<210> 96  
 <211> 166  
 <212> PRT  
 <213> Homo sapiens

```

<400> 96
Met Ala Gln Thr Asn Ser Phe Phe Met Leu Ile Ser Ser Leu Met Phe
  1      5      10      15
Leu Ser Leu Ser Gln Gly Gln Glu Ser Gln Thr Glu Leu Pro Asn Pro
      20      25      30
Arg Ile Ser Cys Pro Glu Gly Thr Asn Ala Tyr Arg Ser Tyr Cys Tyr
      35      40      45
Tyr Phe Asn Glu Asp Pro Glu Thr Trp Val Asp Ala Asp Leu Tyr Cys
      50      55      60
Gln Asn Met Asn Ser Gly Asn Leu Val Ser Val Leu Thr Gln Ala Glu
      65      70      75      80
Gly Ala Phe Val Ala Ser Leu Ile Lys Glu Ser Ser Thr Asp Asp Ser
      85      90      95
Asn Val Trp Ile Gly Leu His Asp Pro Lys Lys Asn Arg Arg Trp His
      100      105      110
Trp Ser Ser Gly Ser Leu Val Ser Tyr Lys Ser Trp Asp Thr Gly Ser
      115      120      125
Pro Ser Ser Ala Asn Ala Gly Tyr Cys Ala Ser Leu Thr Ser Cys Ser
      130      135      140
Gly Phe Lys Lys Trp Lys Asp Glu Ser Cys Glu Lys Lys Phe Ser Phe
      145      150      155      160
Val Cys Lys Phe Lys Asn
      165

```

<210> 97  
 <211> 411  
 <212> PRT  
 <213> Homo sapiens

```

<400> 97
Met Trp Ser Gly Trp Trp Leu Trp Pro Leu Val Ala Val Cys Thr Ala
  1      5      10      15
Asp Phe Phe Arg Asp Glu Ala Glu Arg Ile Met Arg Asp Ser Pro Val
      20      25      30
Ile Asp Gly His Asn Asp Leu Pro Trp Gln Leu Leu Asp Met Phe Asn
      35      40      45
Asn Arg Leu Gln Asp Glu Arg Ala Asn Leu Thr Thr Leu Ala Gly Thr
      50      55      60
His Thr Asn Ile Pro Lys Leu Arg Ala Gly Phe Val Gly Gly Gln Phe
      65      70      75      80
Trp Ser Val Tyr Thr Pro Cys Asp Thr Gln Asn Lys Asp Ala Val Arg
      85      90      95
Arg Thr Leu Glu Gln Met Asp Val Val His Arg Met Cys Arg Met Tyr
      100      105      110
Pro Glu Thr Phe Leu Tyr Val Thr Ser Ser Ala Gly Ile Arg Gln Ala
      115      120      125
Phe Arg Glu Gly Lys Val Ala Ser Leu Ile Gly Val Glu Gly Gly His
      130      135      140

```

## SEQUENCE LISTING 1657-2022.txt

```

Ser Ile Asp Ser Ser Leu Gly Val Leu Arg Ala Leu Tyr Gln Leu Gly
145      150      155      160
Met Arg Tyr Leu Thr Leu Thr His Ser Cys Asn Thr Pro Trp Ala Asp
      165      170      175
Asn Trp Leu Val Asp Thr Gly Asp Ser Glu Pro Gln Ser Gln Gly Leu
      180      185      190
Ser Pro Phe Gly Gln Arg Val Val Lys Glu Leu Asn Arg Leu Gly Val
      195      200      205
Leu Ile Asp Leu Ala His Val Ser Val Ala Thr Met Lys Ala Thr Leu
      210      215      220
Gln Leu Ser Arg Ala Pro Val Ile Phe Ser His Ser Ser Ala Tyr Ser
      225      230      235
Val Cys Ala Ser Arg Arg Asn Val Pro Asp Asp Val Leu Arg Leu Val
      240      245      250
Lys Gln Thr Asp Ser Leu Val Met Val Asn Phe Tyr Asn Asn Tyr Ile
      255      260      265
Ser Cys Thr Asn Lys Ala Asn Leu Ser Gln Val Ala Asp His Leu Asp
      270      275      280
His Ile Lys Glu Val Ala Gly Ala Arg Ala Val Gly Phe Gly Gly Asp
      285      290      295
Phe Asp Gly Val Pro Arg Val Pro Glu Gly Leu Glu Asp Val Ser Lys
      300      305      310
Tyr Pro Asp Leu Ile Ala Glu Leu Leu Arg Arg Asn Trp Thr Glu Ala
      315      320      325
Glu Val Lys Gly Ala Leu Ala Asp Asn Leu Leu Arg Val Phe Glu Ala
      330      335      340
Val Glu Gln Ala Ser Asn Leu Thr Gln Ala Pro Glu Glu Glu Pro Ile
      345      350      355
Pro Leu Asp Gln Leu Gly Gly Ser Cys Arg Thr His Tyr Gly Tyr Ser
      360      365      370
Ser Gly Ala Ser Ser Leu His Arg His Trp Gly Leu Leu Leu Ala Ser
      375      380      385
Leu Ala Pro Leu Val Leu Cys Leu Ser Leu Leu
      390      395      400
      405      410

```

<210> 98  
 <211> 99  
 <212> PRT  
 <213> Homo sapiens

<400> 98  
 Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser  
 1 5 10 15  
 Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu  
 20 25 30  
 Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe  
 35 40 45  
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr  
 50 55 60  
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro  
 65 70 75 80  
 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala  
 85 90 95  
 Glu Asn Ser

<210> 99  
 <211> 469  
 <212> PRT  
 <213> Homo sapiens

<400> 99  
 Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val  
 1 5 10 15  
 Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp

## SEQUENCE LISTING 1657-2022.txt

20 25 30  
 Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly  
 35 40 45  
 Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu  
 50 55 60  
 Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp  
 65 70 75 80  
 Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr  
 100 105 110  
 His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala  
 115 120 125  
 Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val  
 130 135 140  
 Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met  
 145 150 155 160  
 Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly  
 165 170 175  
 Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg  
 195 200 205  
 Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu  
 210 215 220  
 Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr  
 225 230 235 240  
 Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile  
 245 250 255  
 Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro  
 260 265 270  
 Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr  
 275 280 285  
 Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg  
 290 295 300  
 Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe  
 305 310 315 320  
 Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp  
 325 330 335  
 Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln  
 340 345 350  
 Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe  
 355 360 365  
 Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu  
 370 375 380  
 Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr  
 385 390 395 400  
 Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala  
 405 410 415  
 His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys  
 420 425 430  
 Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp  
 435 440 445  
 Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe  
 450 455 460  
 Asn Cys Arg Lys Asn  
 465

<210> 100  
 <211> 267  
 <212> PRT  
 <213> Homo sapiens

<400> 100  
 Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu  
 1 5 10 15

## SEQUENCE LISTING 1657-2022.txt

Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp  
 20 25 30  
 Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu  
 35 40 45  
 Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys  
 50 55 60  
 Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu  
 65 70 75 80  
 Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser  
 85 90 95  
 Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg  
 100 105 110  
 Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu  
 115 120 125  
 Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe  
 130 135 140  
 Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg  
 145 150 155 160  
 Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu  
 165 170 175  
 Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe  
 180 185 190  
 Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe  
 195 200 205  
 Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His  
 210 215 220  
 Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp  
 225 230 235 240  
 Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys  
 245 250 255  
 Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys  
 260 265

<210> 101  
 <211> 300  
 <212> PRT  
 <213> Homo sapiens

<400> 101  
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
 1 5 10 15  
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu  
 20 25 30  
 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro  
 35 40 45  
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser  
 50 55 60  
 Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp  
 65 70 75 80  
 Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp  
 85 90 95  
 Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser  
 100 105 110  
 Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala  
 115 120 125  
 Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly  
 130 135 140  
 Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe  
 145 150 155 160  
 Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr  
 165 170 175  
 Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro  
 180 185 190  
 Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys  
 195 200 205  
 Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His

## SEQUENCE LISTING 1657-2022.txt

210  
 Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser  
 225  
 Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser  
 230  
 Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val  
 245  
 Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile  
 250  
 Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn  
 260  
 270  
 280  
 290  
 295  
 300

<210> 102  
 <211> 98  
 <212> PRT  
 <213> Homo sapiens

<400> 102  
 Met Asn Gln Thr Ala Ile Leu Ile Cys Cys Leu Ile Phe Leu Thr Leu  
 1  
 Ser Gly Ile Gln Gly Val Pro Leu Ser Arg Thr Val Arg Cys Thr Cys  
 5  
 Ile Ser Ile Ser Asn Gln Pro Val Asn Pro Arg Ser Leu Glu Lys Leu  
 10  
 Glu Ile Ile Pro Ala Ser Gln Phe Cys Pro Arg Val Glu Ile Ile Ala  
 15  
 Thr Met Lys Lys Lys Gly Glu Lys Arg Cys Leu Asn Pro Glu Ser Lys  
 20  
 Ala Ile Lys Asn Leu Leu Lys Ala Val Ser Lys Glu Met Ser Lys Arg  
 25  
 Ser Pro  
 30  
 35  
 40  
 45  
 50  
 55  
 60  
 65  
 70  
 75  
 80  
 85  
 90  
 95

<210> 103  
 <211> 871  
 <212> PRT  
 <213> Homo sapiens

<400> 103  
 Met Lys Tyr Ser Cys Cys Ala Leu Val Leu Ala Val Leu Gly Thr Glu  
 1  
 Leu Leu Gly Ser Leu Cys Ser Thr Val Arg Ser Pro Arg Phe Arg Gly  
 5  
 Arg Ile Gln Gln Glu Arg Lys Asn Ile Arg Pro Asn Ile Ile Leu Val  
 10  
 Pro Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Leu Gln Val Met Asn  
 15  
 Lys Thr Arg Lys Ile Met Glu His Gly Gly Ala Thr Phe Ile Asn Ala  
 20  
 Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Met Leu Thr  
 25  
 Gly Lys Tyr Val His Asn His Asn Val Tyr Thr Asn Asn Glu Asn Cys  
 30  
 Ser Ser Pro Ser Trp Gln Ala Met His Glu Pro Arg Thr Phe Ala Val  
 35  
 Tyr Leu Asn Asn Thr Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr Leu  
 40  
 Asn Glu Tyr Asn Gly Ser Tyr Ile Pro Pro Gly Trp Arg Glu Trp Leu  
 45  
 Gly Leu Ile Lys Asn Ser Arg Phe Tyr Asn Tyr Thr Val Cys Arg Asn  
 50  
 Gly Ile Lys Glu Lys His Gly Phe Asp Tyr Ala Lys Asp Tyr Phe Thr  
 55  
 Asp Leu Ile Thr Asn Glu Ser Ile Asn Tyr Phe Lys Met Ser Lys Arg  
 60  
 65  
 70  
 75  
 80  
 85  
 90  
 95  
 100  
 105  
 110  
 115  
 120  
 125  
 130  
 135  
 140  
 145  
 150  
 155  
 160  
 165  
 170  
 175  
 180  
 185  
 190  
 195  
 200  
 205

## SEQUENCE LISTING 1657-2022.txt

```

Met Tyr Pro His Arg Pro Val Met Met Val Ile Ser His Ala Ala Pro
210 215 220
His Gly Pro Glu Asp Ser Ala Pro Gln Phe Ser Lys Leu Tyr Pro Asn
225 230 235 240
Ala Ser Gln His Ile Thr Pro Ser Tyr Asn Tyr Ala Pro Asn Met Asp
245 250 255
Lys His Trp Ile Met Gln Tyr Thr Gly Pro Met Leu Pro Ile His Met
260 265 270
Glu Phe Thr Asn Ile Leu Gln Arg Lys Arg Leu Gln Thr Leu Met Ser
275 280 285
Val Asp Asp Ser Val Glu Arg Leu Tyr Asn Met Leu Val Glu Thr Gly
290 295 300
Glu Leu Glu Asn Thr Tyr Ile Ile Tyr Thr Ala Asp His Gly Tyr His
305 310 315 320
Ile Gly Gln Phe Gly Leu Val Lys Gly Lys Ser Met Pro Tyr Asp Phe
325 330 335
Asp Ile Arg Val Pro Phe Phe Ile Arg Gly Pro Ser Val Glu Pro Gly
340 345 350
Ser Ile Val Pro Gln Ile Val Leu Asn Ile Asp Leu Ala Pro Thr Ile
355 360 365
Leu Asp Ile Ala Gly Leu Asp Thr Pro Pro Asp Val Asp Gly Lys Ser
370 375 380
Val Leu Lys Leu Leu Asp Pro Glu Lys Pro Gly Asn Arg Phe Arg Thr
385 390 395 400
Asn Lys Lys Ala Lys Ile Trp Arg Asp Thr Phe Leu Val Glu Arg Gly
405 410 415
Lys Phe Leu Arg Lys Lys Glu Glu Ser Ser Lys Asn Ile Gln Gln Ser
420 425 430
Asn His Leu Pro Lys Tyr Glu Arg Val Lys Glu Leu Cys Gln Gln Ala
435 440 445
Arg Tyr Gln Thr Ala Cys Glu Gln Pro Gly Gln Lys Trp Gln Cys Ile
450 455 460
Glu Asp Thr Ser Gly Lys Leu Arg Ile His Lys Cys Lys Gly Pro Ser
465 470 475 480
Asp Leu Leu Thr Val Arg Gln Ser Thr Arg Asn Leu Tyr Ala Arg Gly
485 490 495
Phe His Asp Lys Asp Lys Glu Cys Ser Cys Arg Glu Ser Gly Tyr Arg
500 505 510
Ala Ser Arg Ser Gln Arg Lys Ser Gln Arg Gln Phe Leu Arg Asn Gln
515 520 525
Gly Thr Pro Lys Tyr Lys Pro Arg Phe Val His Thr Arg Gln Thr Arg
530 535 540
Ser Leu Ser Val Glu Phe Glu Gly Glu Ile Tyr Asp Ile Asn Leu Glu
545 550 555 560
Glu Glu Glu Glu Leu Gln Val Leu Gln Pro Arg Asn Ile Ala Lys Arg
565 570 575
His Asp Glu Gly His Lys Gly Pro Arg Asp Leu Gln Ala Ser Ser Gly
580 585 590
Gly Asn Arg Gly Arg Met Leu Ala Asp Ser Ser Asn Ala Val Gly Pro
595 600 605
Pro Thr Thr Val Arg Val Thr His Lys Cys Phe Ile Leu Pro Asn Asp
610 615 620
Ser Ile His Cys Glu Arg Glu Leu Tyr Gln Ser Ala Arg Ala Trp Lys
625 630 635 640
Asp His Lys Ala Tyr Ile Asp Lys Glu Ile Glu Ala Leu Gln Asp Lys
645 650 655
Ile Lys Asn Leu Arg Glu Val Arg Gly His Leu Lys Arg Arg Lys Pro
660 665 670
Glu Glu Cys Ser Cys Ser Lys Gln Ser Tyr Tyr Asn Lys Glu Lys Gly
675 680 685
Val Lys Lys Gln Glu Lys Leu Lys Ser His Leu His Pro Phe Lys Glu
690 695 700
Ala Ala Gln Glu Val Asp Ser Lys Leu Gln Leu Phe Lys Glu Asn Asn
705 710 715 720
Arg Arg Arg Lys Lys Glu Arg Lys Glu Lys Arg Arg Gln Arg Lys Gly
725 730 735
Glu Glu Cys Ser Leu Pro Gly Leu Thr Cys Phe Thr His Asp Asn Asn

```

## SEQUENCE LISTING 1657-2022.txt

740  
 His Trp Gln Thr Ala Pro Phe Trp Asn Leu Gly Ser Phe Cys Ala Cys  
 755  
 Thr Ser Ser Asn Asn Asn Thr Tyr Trp Cys Leu Arg Thr Val Asn Glu  
 770  
 Thr His Asn Phe Leu Phe Cys Glu Phe Ala Thr Gly Phe Leu Glu Tyr  
 785  
 Phe Asp Met Asn Thr Asp Pro Tyr Gln Leu Thr Asn Thr Val His Thr  
 800  
 Val Glu Arg Gly Ile Leu Asn Gln Leu His Val Gln Leu Met Glu Leu  
 815  
 Arg Ser Cys Gln Gly Tyr Lys Gln Cys Asn Pro Arg Pro Lys Asn Leu  
 830  
 Asp Val Gly Asn Lys Asp Gly Gly Ser Tyr Asp Leu His Arg Gly Gln  
 845  
 Leu Trp Asp Gly Trp Glu Gly  
 860  
 865  
 870

<210> 104  
 <211> 1496  
 <212> PRT  
 <213> Homo sapiens

<400> 104  
 Met Met Ala Asn Trp Ala Glu Ala Arg Pro Leu Leu Ile Leu Ile Val  
 1 5 10 15  
 Leu Leu Gly Gln Phe Val Ser Ile Lys Ala Gln Glu Glu Asp Glu Asp  
 20 25 30  
 Glu Gly Tyr Gly Glu Glu Ile Ala Cys Thr Gln Asn Gly Gln Met Tyr  
 35 40 45  
 Leu Asn Arg Asp Ile Trp Lys Pro Ala Pro Cys Gln Ile Cys Val Cys  
 50 55 60  
 Asp Asn Gly Ala Ile Leu Cys Asp Lys Ile Glu Cys Gln Asp Val Leu  
 65 70 75 80  
 Asp Cys Ala Asp Pro Val Thr Pro Pro Gly Glu Cys Cys Pro Val Cys  
 85 90 95  
 Ser Gln Thr Pro Gly Gly Gly Asn Thr Asn Phe Gly Arg Gly Arg Lys  
 100 105 110  
 Gly Gln Lys Gly Glu Pro Gly Leu Val Pro Val Val Thr Gly Ile Arg  
 115 120 125  
 Gly Arg Pro Gly Pro Ala Gly Pro Pro Gly Ser Gln Gly Pro Arg Gly  
 130 135 140  
 Glu Arg Gly Pro Lys Gly Arg Pro Gly Pro Arg Gly Pro Gln Gly Ile  
 145 150 155 160  
 Asp Gly Glu Pro Gly Val Pro Gly Gln Pro Gly Ala Pro Gly Pro Pro  
 165 170 175  
 Gly His Pro Ser His Pro Gly Pro Asp Gly Leu Ser Arg Pro Phe Ser  
 180 185 190  
 Ala Gln Met Ala Gly Leu Asp Glu Lys Ser Gly Leu Gly Ser Gln Val  
 195 200 205  
 Gly Leu Met Pro Gly Ser Val Gly Pro Val Gly Pro Arg Gly Pro Gln  
 210 215 220  
 Gly Leu Gln Gly Gln Gln Gly Gly Ala Gly Pro Thr Gly Pro Pro Gly  
 225 230 235 240  
 Glu Pro Gly Asp Pro Gly Pro Met Gly Pro Ile Gly Ser Arg Gly Pro  
 245 250 255  
 Glu Gly Pro Pro Gly Lys Pro Gly Glu Asp Gly Glu Pro Gly Arg Asn  
 260 265 270  
 Gly Asn Pro Gly Glu Val Gly Phe Ala Gly Ser Pro Gly Ala Arg Gly  
 275 280 285  
 Phe Pro Gly Ala Pro Gly Leu Pro Gly Leu Lys Gly His Arg Gly His  
 290 295 300  
 Lys Gly Leu Glu Gly Pro Lys Gly Glu Val Gly Ala Pro Gly Ser Lys  
 305 310 315 320  
 Gly Glu Ala Gly Pro Thr Gly Pro Met Gly Ala Met Gly Pro Leu Gly  
 325 330 335



## SEQUENCE LISTING 1657-2022.txt

Pro Arg Gly Met Pro Gly Glu Arg Gly Arg Leu Gly Pro Gln Gly Ala  
 340 345 350  
 Pro Gly Gln Arg Gly Ala His Gly Met Pro Gly Lys Pro Gly Pro Met  
 355 360 365  
 Gly Pro Leu Gly Ile Pro Gly Ser Ser Gly Phe Pro Gly Asn Pro Gly  
 370 375 380  
 Met Lys Gly Glu Ala Gly Pro Thr Gly Ala Arg Gly Pro Glu Gly Pro  
 385 390 395 400  
 Gln Gly Gln Arg Gly Glu Thr Gly Pro Pro Gly Pro Val Gly Ser Pro  
 405 410 415  
 Gly Leu Pro Gly Ala Ile Gly Thr Asp Gly Thr Pro Gly Pro Lys Gly  
 420 425 430  
 Pro Thr Gly Ser Pro Gly Thr Ser Gly Pro Pro Gly Ser Ala Gly Pro  
 435 440 445  
 Pro Gly Ser Pro Gly Pro Gln Gly Ser Thr Gly Pro Gln Gly Asn Ser  
 450 455 460  
 Gly Leu Pro Gly Asp Pro Gly Phe Lys Gly Glu Ala Gly Pro Lys Gly  
 465 470 475 480  
 Glu Pro Gly Pro His Gly Ile Gln Gly Pro Ile Gly Pro Pro Gly Glu  
 485 490 495  
 Glu Gly Lys Arg Gly Pro Arg Gly Asp Pro Gly Thr Leu Gly Pro Pro  
 500 505 510  
 Gly Pro Val Gly Glu Arg Gly Ala Pro Gly Asn Arg Gly Phe Pro Gly  
 515 520 525  
 Ser Asp Gly Leu Pro Gly Pro Lys Gly Ala Gln Gly Asp Pro Gly Arg Pro  
 530 535 540  
 Val Gly Ser Ser Gly Pro Lys Gly Ser Gln Gly Asp Pro Gly Arg Pro  
 545 550 555 560  
 Gly Glu Pro Gly Leu Pro Gly Ala Arg Gly Leu Thr Gly Asn Pro Gly  
 565 570 575  
 Val Gln Gly Pro Glu Gly Lys Leu Gly Pro Leu Gly Ala Pro Gly Glu  
 580 585 590  
 Asp Gly Arg Pro Gly Pro Pro Gly Ser Ile Gly Ile Lys Gly Gln Pro  
 595 600 605  
 Gly Thr Met Gly Leu Pro Gly Pro Lys Gly Ser Asn Gly Asp Pro Gly  
 610 615 620  
 Lys Pro Gly Glu Ala Gly Asn Pro Gly Val Pro Gly Gln Arg Gly Ala  
 625 630 635 640  
 Pro Gly Lys Asp Gly Lys Val Gly Pro Tyr Gly Pro Pro Gly Pro Pro  
 645 650 655  
 Gly Leu Arg Gly Glu Arg Gly Glu Gln Gly Pro Pro Gly Pro Thr Gly  
 660 665 670  
 Phe Gln Gly His Pro Gly Pro Pro Gly Pro Pro Gly Glu Gly Gly Lys  
 675 680 685  
 Pro Gly Asp Gln Gly Val Pro Gly Gly Pro Gly Ala Val Gly Pro Leu  
 690 695 700  
 Gly Pro Arg Gly Glu Arg Gly Asn Pro Gly Glu Arg Gly Glu Pro Gly  
 705 710 715 720  
 Ile Thr Gly Leu Pro Gly Glu Lys Gly Met Ala Gly Gly His Gly Pro  
 725 730 735  
 Asp Gly Pro Lys Gly Ser Pro Gly Pro Ser Gly Thr Pro Gly Asp Thr  
 740 745 750  
 Gly Pro Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ile Ala Gly  
 755 760 765  
 Thr Pro Gly Pro Lys Gly Asp Arg Gly Gly Ile Gly Glu Lys Gly Ala  
 770 775 780  
 Glu Gly Thr Ala Gly Asn Asp Gly Ala Gly Gly Leu Pro Gly Pro Leu  
 785 790 795 800  
 Gly Pro Pro Gly Pro Ala Gly Leu Leu Gly Glu Lys Gly Glu Pro Gly  
 805 810 815  
 Pro Arg Gly Leu Val Gly Pro Pro Gly Ser Arg Gly Asn Pro Gly Ser  
 820 825 830  
 Arg Gly Glu Asn Gly Pro Thr Gly Ala Val Gly Phe Ala Gly Pro Gln  
 835 840 845  
 Gly Ser Asp Gly Gln Pro Gly Val Lys Gly Glu Pro Gly Glu Pro Gly  
 850 855 860  
 Gln Lys Gly Asp Ala Gly Ser Pro Gly Pro Gln Gly Leu Ala Gly Ser

## SEQUENCE LISTING 1657-2022.txt

865 Pro Gly Pro His Gly 870 Pro Asn Gly Val 875 Pro Gly Leu Lys Gly Gly Arg 880  
 Gly Thr Gln Gly 885 Pro Pro Gly Ala Thr 890 Gly Phe Pro Gly Ser Ala Gly 895  
 Arg Val Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Pro Ala Gly Pro 900  
 Leu Gly Glu Pro Gly Lys 905 Gly Val Arg Gly Pro Ala Gly Pro Pro Gly 910  
 Gly Ser His Gly Arg Val Gly Val Arg Gly Pro Ala Gly Pro Pro Gly 915  
 Gly Pro Gly Asp Lys 920 Gly Asp Pro Gly Glu Asp Gly Gln Pro Gly Pro 925  
 Asp Gly Pro Pro Gly Pro Ala Gly Thr Thr Gly Gln Arg Gly Ile Val 930  
 Gly Met Pro Gly Gln Arg Gly Glu Arg Gly Met Pro Gly Leu Pro Gly 935  
 Pro Ala Gly Thr Pro Gly Lys Val Gly Pro Thr Gly Ala Thr Gly Asp 940  
 Lys Gly Pro Pro Gly Pro Val Gly Pro Pro Gly Ser Asn Gly Pro Val 945  
 Gly Glu Pro Gly Pro Glu Gly Pro Ala Gly Asn Asp Gly Thr Pro Gly 950  
 Arg Asp Gly Ala Val Gly Glu Arg Gly Asp Arg Gly Asp Pro Gly Pro 955  
 Ala Gly Leu Pro Gly Ser Gln Gly Ala Pro Gly Thr Pro Gly Pro Val 960  
 Gly Ala Pro Gly Asp Ala Gly Gln Arg Gly Asp Pro Gly Ser Arg Gly 965  
 Pro Ile Gly His Leu Gly Arg Ala Gly Lys Arg Gly Leu Pro Gly Pro 970  
 Gln Gly Pro Arg Gly Asp Lys Gly Asp His Gly Asp Arg Gly Asp Arg 975  
 Gly Gln Lys Gly His Arg Gly Phe Thr Gly Leu Gln Gly Leu Pro Gly 980  
 Pro Pro Gly Pro Asn Gly Glu Gln Gly Ser Ala Gly Ile Pro Gly Pro 985  
 Phe Gly Pro Arg Gly Pro Pro Gly Pro Val Gly Pro Ser Gly Lys Glu 990  
 Gly Asn Pro Gly Pro Leu Gly Pro Leu Gly Pro Pro Gly Val Arg Gly 995  
 Ser Val Gly Glu Ala Gly Pro Glu Gly Pro Pro Gly Glu Pro Gly Pro 1000  
 Pro Gly Pro Pro Gly Pro Pro Gly His Leu Thr Ala Ala Leu Gly Asp 1005  
 Ile Met Gly His Tyr Asp Glu Ser Met Pro Asp Pro Leu Pro Glu Phe 1010  
 Thr Glu Asp Gln Ala Ala Pro Asp Asp Lys Asn Lys Thr Asp Pro Gly 1015  
 Val His Ala Thr Leu Lys Ser Leu Ser Ser Gln Ile Glu Thr Met Arg 1020  
 Ser Pro Asp Gly Ser Lys Lys His Pro Ala Arg Thr Cys Asp Asp Leu 1025  
 Lys Leu Cys His Ser Ala Lys Gln Ser Gly Glu Tyr Trp Ile Asp Pro 1030  
 Asn Gln Gly Ser Val Glu Asp Ala Ile Lys Val Tyr Cys Asn Met Glu 1035  
 Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Ser Ser Val Pro Arg Lys 1040  
 Thr Trp Trp Ala Ser Lys Ser Pro Asp Asn Lys Pro Val Trp Tyr Gly 1045  
 Leu Asp Met Asn Arg Gly Ser Gln Phe Ala Tyr Gly Asp His Gln Ser 1050  
 Pro Asn Thr Ala Ile Thr Gln Met Thr Phe Leu Arg Leu Leu Ser Lys 1055  
 Glu Ala Ser Gln Asn Ile Thr Tyr Ile Cys Lys Asn Ser Val Gly Tyr 1060  
 1395 1400 1405

## SEQUENCE LISTING 1657-2022.txt

Met Asp Asp Gln Ala Lys Asn Leu Lys Lys Ala Val Val Leu Lys Gly  
 1410 1415 1420  
 Ala Asn Asp Leu Asp Ile Lys Ala Glu Gly Asn Ile Arg Phe Arg Tyr  
 1425 1430 1435 1440  
 Ile Val Leu Gln Asp Thr Cys Ser Lys Arg Asn Gly Asn Val Gly Lys  
 1445 1450 1455  
 Thr Val Phe Glu Tyr Arg Thr Gln Asn Val Ala Arg Leu Pro Ile Ile  
 1460 1465 1470  
 Asp Leu Ala Pro Val Asp Val Gly Gly Thr Asp Gln Glu Phe Gly Val  
 1475 1480 1485  
 Glu Ile Gly Pro Val Cys Phe Val  
 1490 1495

<210> 105  
 <211> 107  
 <212> PRT  
 <213> Homo sapiens

<400> 105  
 Met Ala Arg Ala Ala Leu Ser Ala Ala Pro Ser Asn Pro Arg Leu Leu  
 1 5 10 15  
 Arg Val Ala Leu Leu Leu Leu Leu Val Ala Ala Gly Arg Arg Ala  
 20 25 30  
 Ala Gly Ala Ser Val Ala Thr Glu Leu Arg Cys Gln Cys Leu Gln Thr  
 35 40 45  
 Leu Gln Gly Ile His Pro Lys Asn Ile Gln Ser Val Asn Val Lys Ser  
 50 55 60  
 Pro Gly Pro His Cys Ala Gln Thr Glu Val Ile Ala Thr Leu Lys Asn  
 65 70 75 80  
 Gly Arg Lys Ala Cys Leu Asn Pro Ala Ser Pro Ile Val Lys Lys Ile  
 85 90 95  
 Ile Glu Lys Met Leu Asn Ser Asp Lys Ser Asn  
 100 105

<210> 106  
 <211> 89  
 <212> PRT  
 <213> Homo sapiens

<400> 106  
 Met Lys Gly Leu Ala Ala Ala Leu Leu Val Leu Val Cys Thr Met Ala  
 1 5 10 15  
 Leu Cys Ser Cys Ala Gln Val Gly Thr Asn Lys Glu Leu Cys Cys Leu  
 20 25 30  
 Val Tyr Thr Ser Trp Gln Ile Pro Gln Lys Phe Ile Val Asp Tyr Ser  
 35 40 45  
 Glu Thr Ser Pro Gln Cys Pro Lys Pro Gly Val Ile Leu Leu Thr Lys  
 50 55 60  
 Arg Gly Arg Gln Ile Cys Ala Asp Pro Asn Lys Lys Trp Val Gln Lys  
 65 70 75 80  
 Tyr Ile Ser Asp Leu Lys Leu Asn Ala  
 85

<210> 107  
 <211> 796  
 <212> PRT  
 <213> Homo sapiens

<400> 107  
 Met Lys Glu Asn Tyr Cys Leu Gln Ala Ala Leu Val Cys Leu Gly Met  
 1 5 10 15  
 Leu Cys His Ser His Ala Phe Ala Pro Glu Arg Arg Gly His Leu Arg  
 20 25 30  
 Pro Ser Phe His Gly His His Glu Lys Gly Lys Glu Gly Gln Val Leu  
 Page 81

## SEQUENCE LISTING 1657-2022.txt

35 40 45  
 Gln Arg Ser Lys Arg Gly Trp Val Trp Asn Gln Phe Phe Val Ile Glu  
 50 55 60  
 Glu Tyr Thr Gly Pro Asp Pro Val Leu Val Gly Arg Leu His Ser Asp  
 65 70 75 80  
 Ile Asp Ser Gly Asp Gly Asn Ile Lys Tyr Ile Leu Ser Gly Glu Gly  
 85 90 95  
 Ala Gly Thr Ile Phe Val Ile Asp Asp Lys Ser Gly Asn Ile His Ala  
 100 105 110  
 Thr Lys Thr Leu Asp Arg Glu Glu Arg Ala Gln Tyr Thr Leu Met Ala  
 115 120 125  
 Gln Ala Val Asp Arg Asp Thr Asn Arg Pro Leu Glu Pro Pro Ser Glu  
 130 135 140  
 Phe Ile Val Lys Val Gln Asp Ile Asn Asp Asn Pro Pro Glu Phe Leu  
 145 150 155 160  
 His Glu Thr Tyr His Ala Asn Val Pro Glu Arg Ser Asn Val Gly Thr  
 165 170 175  
 Ser Val Ile Gln Val Thr Ala Ser Asp Ala Asp Asp Pro Thr Tyr Gly  
 180 185 190  
 Asn Ser Ala Lys Leu Val Tyr Ser Ile Leu Glu Gly Gln Pro Tyr Phe  
 195 200 205  
 Ser Val Glu Ala Gln Thr Gly Ile Ile Arg Thr Ala Leu Pro Asn Met  
 210 215 220  
 Asp Arg Glu Ala Lys Glu Glu Tyr His Val Val Ile Gln Ala Lys Asp  
 225 230 235 240  
 Met Gly Gly His Met Gly Gly Leu Ser Gly Thr Thr Lys Val Thr Ile  
 245 250 255  
 Thr Leu Thr Asp Val Asn Asp Asn Pro Pro Lys Phe Pro Gln Ser Val  
 260 265 270  
 Tyr Gln Met Ser Val Ser Glu Ala Val Pro Gly Glu Glu Val Gly  
 275 280 285  
 Arg Val Lys Ala Lys Asp Pro Asp Ile Gly Glu Asn Gly Leu Val Thr  
 290 295 300  
 Tyr Asn Ile Val Asp Gly Asp Gly Met Glu Ser Phe Glu Ile Thr Thr  
 305 310 315 320  
 Asp Tyr Glu Thr Gln Glu Gly Val Ile Lys Leu Lys Lys Pro Val Asp  
 325 330 335  
 Phe Glu Thr Lys Arg Ala Tyr Ser Leu Lys Val Glu Ala Ala Asn Val  
 340 345 350  
 His Ile Asp Pro Lys Phe Ile Ser Asn Gly Pro Phe Lys Asp Thr Val  
 355 360 365  
 Thr Val Lys Ile Ser Val Glu Asp Ala Asp Glu Pro Pro Met Phe Leu  
 370 375 380  
 Ala Pro Ser Tyr Ile His Glu Val Gln Glu Asn Ala Ala Ala Gly Thr  
 385 390 395 400  
 Val Val Gly Arg Val His Ala Lys Asp Pro Asp Ala Ala Asn Ser Pro  
 405 410 415  
 Ile Arg Tyr Ser Ile Asp Arg His Thr Asp Leu Asp Arg Phe Phe Thr  
 420 425 430  
 Ile Asn Pro Glu Asp Gly Phe Ile Lys Thr Thr Lys Pro Leu Asp Arg  
 435 440 445  
 Glu Glu Thr Ala Trp Leu Asn Ile Thr Val Phe Ala Ala Glu Ile His  
 450 455 460  
 Asn Arg His Gln Glu Ala Lys Val Pro Val Ala Ile Arg Val Leu Asp  
 465 470 475 480  
 Val Asn Asp Asn Ala Pro Lys Phe Ala Ala Pro Tyr Glu Gly Phe Ile  
 485 490 495  
 Cys Glu Ser Asp Gln Thr Lys Pro Leu Ser Asn Gln Pro Ile Val Thr  
 500 505 510  
 Ile Ser Ala Asp Asp Lys Asp Asp Thr Ala Asn Gly Pro Arg Phe Ile  
 515 520 525  
 Phe Ser Leu Pro Pro Glu Ile Ile His Asn Pro Asn Phe Thr Val Arg  
 530 535 540  
 Asp Asn Arg Asp Asn Thr Ala Gly Val Tyr Ala Arg Arg Gly Gly Phe  
 545 550 555 560  
 Ser Arg Gln Lys Gln Asp Leu Tyr Leu Leu Pro Ile Val Ile Ser Asp  
 565 570 575

## SEQUENCE LISTING 1657-2022.txt

Gly Gly Ile Pro Pro Met Ser Ser Thr Asn Thr Leu Thr Ile Lys Val  
 580 585 590  
 Cys Gly Cys Asp Val Asn Gly Ala Leu Leu Ser Cys Asn Ala Glu Ala  
 595 600 605  
 Tyr Ile Leu Asn Ala Gly Leu Ser Thr Gly Ala Leu Ile Ala Ile Leu  
 610 615 620  
 Ala Cys Ile Val Ile Leu Leu Val Ile Val Val Leu Phe Val Thr Leu  
 625 630 635 640  
 Arg Arg Gln Lys Lys Glu Pro Leu Ile Val Phe Glu Glu Glu Asp Val  
 645 650 655  
 Arg Glu Asn Ile Ile Thr Tyr Asp Asp Glu Gly Gly Gly Glu Glu Asp  
 660 665 670  
 Thr Glu Ala Phe Asp Ile Ala Thr Leu Gln Asn Pro Asp Gly Ile Asn  
 675 680 685  
 Gly Phe Ile Pro Arg Lys Asp Ile Lys Pro Glu Tyr Gln Tyr Met Pro  
 690 695 700  
 Arg Pro Gly Leu Arg Pro Ala Pro Asn Ser Val Asp Val Asp Asp Phe  
 705 710 715 720  
 Ile Asn Thr Arg Ile Gln Glu Ala Asp Asn Asp Pro Thr Ala Pro Pro  
 725 730 735  
 Tyr Asp Ser Ile Gln Ile Tyr Gly Tyr Glu Gly Arg Gly Ser Val Ala  
 740 745 750  
 Gly Ser Leu Ser Ser Leu Glu Ser Ala Thr Thr Asp Ser Asp Leu Asp  
 755 760 765  
 Tyr Asp Tyr Leu Gln Asn Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp  
 770 775 780  
 Leu Tyr Gly Ser Lys Asp Thr Phe Asp Asp Asp Ser  
 785 790 795

<210> 108  
 <211> 180  
 <212> PRT  
 <213> Homo sapiens

<400> 108  
 Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met Glu Asp Gly  
 1 5 10 15  
 Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile Gly Ile Leu Val Leu Leu  
 20 25 30  
 Ile Ile Val Ile Leu Gly Val Pro Leu Ile Ile Phe Thr Ile Lys Ala  
 35 40 45  
 Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg  
 50 55 60  
 Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly  
 65 70 75 80  
 Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met  
 85 90 95  
 Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys  
 100 105 110  
 Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln  
 115 120 125  
 Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu  
 130 135 140  
 Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser  
 145 150 155 160  
 Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser  
 165 170 175  
 Ala Leu Leu Gln  
 180

<210> 109  
 <211> 358  
 <212> PRT  
 <213> Homo sapiens

## SEQUENCE LISTING 1657-2022.txt

&lt;400&gt; 109

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Met Arg Ala Thr Pro Leu Ala Ala Pro Ala Gly Ser Leu Ser Arg Lys
 1      5      10      15
Lys Arg Leu Glu Leu Asp Asp Asn Leu Asp Thr Glu Arg Pro Val Gln
 20      25      30
Lys Arg Ala Arg Ser Gly Pro Gln Pro Arg Leu Pro Pro Cys Leu Leu
 35      40      45
Pro Leu Ser Pro Pro Thr Ala Pro Asp Arg Ala Thr Ala Val Ala Thr
 50      55      60
Ala Ser Arg Leu Gly Pro Tyr Val Leu Leu Glu Pro Glu Glu Gly Gly
 65      70      75      80
Arg Ala Tyr Gln Ala Leu His Cys Pro Thr Gly Thr Glu Tyr Thr Cys
 85      90      95
Lys Val Tyr Pro Val Gln Glu Ala Pro Ala Val Leu Glu Pro Tyr Ala
100      105      110
Arg Leu Pro Pro His Lys His Val Ala Arg Pro Thr Glu Val Leu Ala
115      120      125
Gly Thr Gln Leu Leu Tyr Ala Phe Phe Thr Arg Thr His Gly Asp Met
130      135      140
His Ser Leu Val Arg Ser Arg His Arg Ile Pro Glu Pro Glu Ala Ala
145      150      155      160
Val Leu Phe Arg Gln Met Ala Thr Ala Leu Ala His Cys His Gln His
165      170      175
Gly Leu Val Leu Arg Asp Leu Lys Leu Cys Arg Phe Val Phe Ala Asp
180      185      190
Arg Glu Arg Lys Lys Leu Val Leu Glu Asn Leu Glu Asp Ser Cys Val
195      200      205
Leu Thr Gly Pro Asp Asp Ser Leu Trp Asp Lys His Ala Cys Pro Ala
210      215      220
Tyr Val Gly Pro Glu Ile Leu Ser Ser Arg Ala Ser Tyr Ser Gly Lys
225      230      235      240
Ala Ala Asp Val Trp Ser Leu Gly Val Ala Leu Phe Thr Met Leu Ala
245      250      255
Gly His Tyr Pro Phe Gln Asp Ser Glu Pro Val Leu Leu Phe Gly Lys
260      265      270
Ile Arg Arg Gly Ala Tyr Ala Leu Pro Ala Gly Leu Ser Ala Pro Ala
275      280      285
Arg Cys Leu Val Arg Cys Leu Leu Arg Arg Glu Pro Ala Glu Arg Leu
290      295      300
Thr Ala Thr Gly Ile Leu Leu His Pro Trp Leu Arg Gln Asp Pro Met
305      310      315      320
Pro Leu Ala Pro Thr Arg Ser His Leu Trp Glu Ala Ala Gln Val Val
325      330      335
Pro Asp Gly Leu Gly Leu Asp Glu Ala Arg Glu Glu Glu Gly Asp Arg
340      345      350
Glu Val Val Leu Tyr Gly
355

```

&lt;210&gt; 110

&lt;211&gt; 1172

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 110

```

Met Val Trp Arg Leu Val Leu Leu Ala Leu Trp Val Trp Pro Ser Thr
 1      5      10      15
Gln Ala Gly His Gln Asp Lys Asp Thr Phe Asp Leu Phe Ser Ile
 20      25      30
Ser Asn Ile Asn Arg Lys Thr Ile Gly Ala Lys Gln Phe Arg Gly Pro
 35      40      45
Asp Pro Gly Val Pro Ala Tyr Arg Phe Val Arg Phe Asp Tyr Ile Pro
 50      55      60
Pro Val Asn Ala Asp Asp Leu Ser Lys Ile Thr Lys Ile Met Arg Gln
 65      70      75      80
Lys Glu Gly Phe Phe Leu Thr Ala Gln Leu Lys Gln Asp Gly Lys Ser
 85      90      95

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## SEQUENCE LISTING 1657-2022.txt

Arg Gly Thr Leu Leu Ala Leu Glu Gly Pro Gly Leu Ser Gln Arg Gln  
 100 105 110  
 Phe Glu Ile Val Ser Asn Gly Pro Ala Asp Thr Leu Asp Leu Thr Tyr  
 115 120 125  
 Trp Ile Asp Gly Thr Arg His Val Val Ser Leu Glu Asp Val Gly Leu  
 130 135 140  
 Ala Asp Ser Gln Trp Lys Asn Val Thr Val Gln Val Ala Gly Glu Thr  
 145 150 155 160  
 Tyr Ser Leu His Val Gly Cys Asp Leu Ile Gly Pro Val Ala Leu Asp  
 165 170 175  
 Glu Pro Phe Tyr Glu His Leu Gln Ala Glu Lys Ser Arg Met Tyr Val  
 180 185 190  
 Ala Lys Gly Ser Ala Arg Glu Ser His Phe Arg Gly Leu Gln Asn  
 195 200 205  
 Val His Leu Val Phe Glu Asn Ser Val Glu Asp Ile Leu Ser Lys Lys  
 210 215 220  
 Gly Cys Gln Gln Gly Gln Gly Ala Glu Ile Asn Ala Ile Ser Glu Asn  
 225 230 235 240  
 Thr Glu Thr Leu Arg Leu Gly Pro His Val Thr Thr Glu Tyr Val Gly  
 245 250 255  
 Pro Ser Ser Glu Arg Arg Pro Glu Val Cys Glu Arg Ser Cys Glu Glu  
 260 265 270  
 Leu Gly Asn Met Val Gln Glu Leu Ser Gly Leu His Val Leu Val Asn  
 275 280 285  
 Gln Leu Ser Glu Asn Leu Lys Arg Val Ser Asn Asp Asn Gln Phe Leu  
 290 295 300  
 Trp Glu Leu Ile Gly Gly Pro Pro Lys Thr Arg Asn Met Ser Ala Cys  
 305 310 315 320  
 Trp Gln Asp Gly Arg Phe Phe Ala Glu Asn Glu Thr Trp Val Val Asp  
 325 330 335  
 Ser Cys Thr Thr Cys Thr Cys Lys Lys Phe Lys Thr Ile Cys His Gln  
 340 345 350  
 Ile Thr Cys Pro Pro Ala Thr Cys Ala Ser Pro Ser Phe Val Glu Gly  
 355 360 365  
 Glu Cys Cys Pro Ser Cys Leu His Ser Val Asp Gly Glu Glu Gly Trp  
 370 375 380  
 Ser Pro Trp Ala Glu Trp Thr Gln Cys Ser Val Thr Cys Gly Ser Gly  
 385 390 395 400  
 Thr Gln Gln Arg Gly Arg Ser Cys Asp Val Thr Ser Asn Thr Cys Leu  
 405 410 415  
 Gly Pro Ser Ile Gln Thr Arg Ala Cys Ser Leu Ser Lys Cys Asp Thr  
 420 425 430  
 Arg Ile Arg Gln Asp Gly Gly Trp Ser His Trp Ser Pro Trp Ser Ser  
 435 440 445  
 Cys Ser Val Thr Cys Gly Val Gly Asn Ile Thr Arg Ile Arg Leu Cys  
 450 455 460  
 Asn Ser Pro Val Pro Gln Met Gly Gly Lys Asn Cys Lys Gly Ser Gly  
 465 470 475 480  
 Arg Glu Thr Lys Ala Cys Gln Gly Ala Pro Cys Pro Ile Asp Gly Arg  
 485 490 495  
 Trp Ser Pro Trp Ser Pro Trp Ser Ala Cys Thr Val Thr Cys Ala Gly  
 500 505 510  
 Gly Ile Arg Glu Arg Thr Arg Val Cys Asn Ser Pro Glu Pro Gln Tyr  
 515 520 525  
 Gly Gly Lys Ala Cys Val Gly Asp Val Gln Glu Arg Gln Met Cys Asn  
 530 535 540  
 Lys Arg Ser Cys Pro Val Asp Gly Cys Leu Ser Asn Pro Cys Phe Pro  
 545 550 555 560  
 Gly Ala Gln Cys Ser Ser Phe Pro Asp Gly Ser Trp Ser Cys Gly Phe  
 565 570 575  
 Cys Pro Val Gly Phe Leu Gly Asn Gly Thr His Cys Glu Asp Leu Asp  
 580 585 590  
 Glu Cys Ala Leu Val Pro Asp Ile Cys Phe Ser Thr Ser Lys Val Pro  
 595 600 605  
 Arg Cys Val Asn Thr Gln Pro Gly Phe His Cys Leu Pro Cys Pro Pro  
 610 615 620  
 Arg Tyr Arg Gly Asn Gln Pro Val Gly Val Gly Leu Glu Ala Ala Lys

## SEQUENCE LISTING 1657-2022.txt

625 Thr Glu Lys Gln Val 630 Cys Glu Pro Glu Asn Pro Cys Lys Asp Lys Thr 640  
 His Asn Cys His 645 His Ala Glu Cys 650 Ile Tyr Leu Gly His 655 Phe Ser  
 Asp Pro Met Tyr Lys Cys Glu Cys 665 Gln Thr Gly Tyr Ala Gly Asp Gly 670  
 Leu Ile 675 Cys Gly Glu Asp Ser 680 Leu Asp Gly Trp Pro Asn Leu Asn 685  
 Leu Val Cys Ala Thr Asn Ala Thr Tyr His Cys Ile Lys Asp Asn Cys 690  
 705 Pro His Leu Pro Asn Ser Gly Gln Glu Asp Phe Asp Lys Asp Gly Ile 710  
 Gly Asp Ala Cys Asp Asp Asp Asp Asn Asp Gly Val Thr Asp Glu 715  
 Lys Asp Asn Cys Gln Leu Leu Phe Asn Pro Arg Gln Ala Asp Tyr Asp 720  
 Lys Asp Glu Val Gly Asp Arg Cys Asp Asn Cys Pro Tyr Val His Asn 725  
 Pro Ala Gln Ile Asp Thr Asp Asn Asn Gly Glu Gly Asp Ala Cys Ser 730  
 Val Asp Ile Asp Gly Asp Asp Val Phe Asn Glu Arg Asp Asn Cys 735  
 Tyr Val Tyr Asn Thr Asp Gln Arg Asp Thr Asp Gly Asp Gly Val Gly 740  
 Asp His Cys Asp Asn Cys Pro Leu Val His Asn Pro Asp Gln Thr Asp 745  
 Val Asp Asn Asp Leu Val Gly Asp Gln Cys Asp Asn Asn Glu Asp Ile 750  
 Asp Asp Asp Gly His Gln Asn Asn Gln Asp Asn Cys Pro Tyr Ile Ser 755  
 Asn Ala Asn Gln Ala Asp His Asp Arg Asp Gly Gln Gly Asp Ala Cys 760  
 Asp Pro Asp Asp Asn Asp Gly Val Pro Asp Asp Arg Asp Asn Cys 765  
 Arg Leu Val Phe Asn Pro Asp Gln Glu Asp Leu Asp Gly Asp Gly Arg 770  
 Gly Asp Ile Cys Lys Asp Asp Phe Asp Asn Asp Asn Ile Pro Asp Ile 775  
 Asp Asp Val Cys Pro Glu Asn Asn Ala Ile Ser Glu Thr Asp Phe Arg 780  
 Asn Phe Gln Met Val Pro Leu Asp Pro Lys Gly Thr Thr Gln Ile Asp 785  
 Pro Asn Trp Val Ile Arg His Gln Gly Lys Glu Leu Val Gln Thr Ala 790  
 Asn Ser Asp Pro Gly Ile Ala Val Gly Phe Asp Glu Phe Gly Ser Val 795  
 Asp Phe Ser Gly Thr Phe Tyr Val Asn Thr Asp Arg Asp Asp Asp Tyr 800  
 Ala Gly Phe Val Phe Gly Tyr Gln Ser Ser Ser Arg Phe Tyr Val Val 805  
 Met Trp Lys Gln Val Thr Gln Thr Tyr Trp Glu Asp Gln Pro Thr Arg 810  
 Ala Tyr Gly Tyr Ser Gly Val Ser Leu Lys Val Val Asn Ser Thr Thr 815  
 Gly Thr Gly Glu His Leu Arg Asn Ala Leu Trp His Thr Gly Asn Thr 820  
 Pro Gly Gln Val Arg Thr Leu Trp His Asp Pro Arg Asn Ile Gly Trp 825  
 Lys Asp Tyr Thr Ala Tyr Arg Trp His Leu Thr His Arg Pro Lys Thr 830  
 1105 Gly Tyr Ile Arg Val Leu Val His Glu Gly Lys Gln Val Met Ala Asp 835  
 Ser Gly Pro Ile Tyr Asp Gln Thr Tyr Ala Gly Gly Arg Leu Gly Leu 840  
 Phe Val Phe Ser Gln Glu Met Val Tyr Phe Ser Asp Leu Lys Tyr Glu 845  
 1155 1160 1165



## SEQUENCE LISTING 1657-2022.txt

Cys Arg Asp Ile  
1170

<210> 111  
<211> 138  
<212> PRT  
<213> Homo sapiens

<400> 111  
Met Arg Gln Lys Ala Val Ser Leu Phe Leu Cys Tyr Leu Leu Leu Phe  
1 5 10 15  
Thr Cys Ser Gly Val Glu Ala Gly Glu Asn Ala Gly Lys Asp Ala Gly  
20 25 30  
Lys Lys Lys Cys Ser Glu Ser Ser Asp Ser Gly Ser Gly Phe Trp Lys  
35 40 45  
Ala Leu Thr Phe Met Ala Val Gly Gly Leu Ala Val Ala Gly Leu  
50 55 60  
Pro Ala Leu Gly Phe Thr Gly Ala Gly Ile Ala Ala Asn Ser Val Ala  
65 70 75 80  
Ala Ser Leu Met Ser Trp Ser Ala Ile Leu Asn Gly Gly Gly Val Pro  
85 90 95  
Ala Gly Gly Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Gly Gly Ser  
100 105 110  
Ser Val Val Ile Gly Asn Ile Gly Ala Leu Met Gly Tyr Ala Thr His  
115 120 125  
Lys Tyr Leu Asp Ser Glu Glu Asp Glu Glu  
130 135

<210> 112  
<211> 184  
<212> PRT  
<213> Homo sapiens

<400> 112  
Met Ser Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly  
1 5 10 15  
Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala  
20 25 30  
Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln  
35 40 45  
Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg  
50 55 60  
Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala  
65 70 75 80  
Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr  
85 90 95  
Gln Pro Leu Lys Gln Thr Ile His Glu Gly Cys Asn Ser Arg Thr  
100 105 110  
Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro  
115 120 125  
Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys  
130 135 140  
Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu  
145 150 155 160  
Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys  
165 170 175  
Arg Cys Ile Ser Ile Asp Leu Asp  
180

<210> 113  
<211> 707  
<212> PRT  
<213> Homo sapiens

## SEQUENCE LISTING 1657-2022.txt

&lt;400&gt; 113

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Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Leu Val Leu Gly Cys
1      5      10      15
Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro
20      25      30
Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
35      40      45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
50      55      60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
65      70      75      80
Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
85      90      95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
100     105     110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
115     120     125
Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
130     135     140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
145     150     155     160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
165     170     175
Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
180     185     190
Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Glu
195     200     205
Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn
210     215     220
Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser
225     230     235     240
Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys
245     250     255
Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro
260     265     270
Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys
275     280     285
Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr
290     295     300
Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr
305     310     315     320
Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr
325     330     335
Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr
340     345     350
Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp
355     360     365
Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys
370     375     380
Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala
385     390     395     400
His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu
405     410     415
Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His
420     425     430
Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu
435     440     445
Pro Glu Pro Arg Pro Thr Thr Thr Pro Gln Pro Thr Ala Pro
450     455     460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
465     470     475     480
Pro Thr Ala Gly Pro Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
485     490     495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
500     505     510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
515     520     525

```

## SEQUENCE LISTING 1657-2022.txt

Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu  
 530 535 540  
 Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp  
 545 550 555 560  
 Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser  
 565 570 575  
 Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly  
 580 585 590  
 Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala  
 595 600 605  
 Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met  
 610 615 620  
 Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln  
 625 630 635 640  
 Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly  
 645 650 655  
 Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr  
 660 665 670  
 Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu  
 675 680 685  
 Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys  
 690 695 700  
 Pro Glu Asp  
 705

<210> 114  
 <211> 194  
 <212> PRT  
 <213> Homo sapiens

<400> 114  
 Met Ala Ile Arg Glu Leu Lys Val Cys Leu Leu Gly Asp Thr Gly Val  
 1 5 10 15  
 Gly Lys Ser Ser Ile Val Cys Arg Phe Val Gln Asp His Phe Asp His  
 20 25 30  
 Asn Ile Ser Pro Thr Ile Gly Ala Ser Phe Met Thr Lys Thr Val Pro  
 35 40 45  
 Cys Gly Asn Glu Leu His Lys Phe Leu Ile Trp Asp Thr Ala Gly Gln  
 50 55 60  
 Glu Arg Phe His Ser Leu Ala Pro Met Tyr Tyr Arg Gly Ser Ala Ala  
 65 70 75 80  
 Ala Val Ile Val Tyr Asp Ile Thr Lys Gln Asp Ser Phe Tyr Thr Leu  
 85 90 95  
 Lys Lys Trp Val Lys Glu Leu Lys Glu His Gly Pro Glu Asn Ile Val  
 100 105 110  
 Met Ala Ile Ala Gly Asn Lys Cys Asp Leu Ser Asp Ile Arg Glu Val  
 115 120 125  
 Pro Leu Lys Asp Ala Lys Glu Tyr Ala Glu Ser Ile Gly Ala Ile Val  
 130 135 140  
 Val Glu Thr Ser Ala Lys Asn Ala Ile Asn Ile Glu Glu Leu Phe Gln  
 145 150 155 160  
 Gly Ile Ser Arg Gln Ile Pro Pro Leu Asp Pro His Glu Asn Gly Asn  
 165 170 175  
 Asn Gly Thr Ile Lys Val Glu Lys Pro Thr Met Gln Ala Ser Arg Arg  
 180 185 190  
 Cys Cys

<210> 115  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 115  
 Met Ser Ala Leu Ser Leu Leu Ile Leu Gly Leu Leu Thr Ala Val Pro  
 Page 89

## SEQUENCE LISTING 1657-2022.txt

```

1           5           10           15
Pro Ala Ser Cys Gln Gln Gly Leu Gly Asn Leu Gln Pro Trp Met Gln
                20           25           30
Gly Leu Ile Ala Val Ala Val Phe Leu Val Leu Val Ala Ile Ala Phe
                35           40           45
Ala Val Asn His Phe Trp Cys Gln Glu Glu Pro Glu Pro Ala His Met
                50           55           60
Ile Leu Thr Val Gly Asn Lys Ala Asp Gly Val Leu Val Gly Thr Asp
65           70           75           80
Gly Arg Tyr Ser Ser Met Ala Ala Ser Phe Arg Ser Ser Glu His Glu
                85           90           95
Asn Ala Tyr Glu Asn Val Pro Glu Glu Gly Lys Val Arg Ser Thr
                100          105          110
Pro Met

```

<210> 116  
 <211> 117  
 <212> PRT  
 <213> Homo sapiens

```

<400> 116
Met Ala Leu Glu Thr Val Pro Lys Asp Leu Arg His Leu Arg Ala Cys
1           5           10           15
Leu Leu Cys Ser Leu Val Lys Thr Ile Asp Gln Phe Glu Tyr Asp Gly
                20           25           30
Cys Asp Asn Cys Asp Ala Tyr Leu Gln Met Lys Gly Asn Arg Glu Met
                35           40           45
Val Tyr Asp Cys Thr Ser Ser Ser Phe Asp Gly Ile Ile Ala Met Met
                50           55           60
Ser Pro Glu Asp Ser Trp Val Ser Lys Trp Gln Arg Val Ser Asn Phe
65           70           75           80
Lys Pro Gly Val Tyr Ala Val Ser Val Thr Gly Arg Leu Pro Gln Gly
                85           90           95
Ile Val Arg Glu Leu Lys Ser Arg Gly Val Ala Tyr Lys Ser Arg Asp
                100          105          110
Thr Ala Ile Lys Thr
                115

```

<210> 117  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens

```

<400> 117
Met Ser Pro Ser Gly Arg Leu Cys Leu Leu Thr Ile Val Gly Leu Ile
1           5           10           15
Leu Pro Thr Arg Gly Gln Thr Leu Lys Asp Thr Thr Ser Ser Ser
                20           25           30
Ala Asp Ser Thr Ile Met Asp Ile Gln Val Pro Thr Arg Ala Pro Asp
                35           40           45
Ala Val Tyr Thr Glu Leu Gln Pro Thr Ser Pro Thr Pro Thr Trp Pro
                50           55           60
Ala Asp Glu Thr Pro Gln Pro Gln Thr Gln Thr Gln Gln Leu Glu Gly
65           70           75           80
Thr Asp Gly Pro Leu Val Thr Asp Pro Glu Thr His Lys Ser Thr Lys
                85           90           95
Ala Ala His Pro Thr Asp Asp Thr Thr Thr Leu Ser Glu Arg Pro Ser
                100          105          110
Pro Ser Thr Asp Val Gln Thr Asp Pro Gln Thr Leu Lys Pro Ser Gly
                115          120          125
Phe His Glu Asp Asp Pro Phe Phe Tyr Asp Glu His Thr Leu Arg Lys
                130          135          140
Arg Gly Leu Leu Val Ala Ala Val Leu Phe Ile Thr Gly Ile Ile Ile
145          150          155          160

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## SEQUENCE LISTING 1657-2022.txt

Leu Thr Ser Gly Lys Cys Arg Gln Leu Ser Arg Leu Cys Arg Asn Arg  
 165 170 175  
 Cys Arg

<210> 118  
 <211> 3396  
 <212> PRT  
 <213> Homo sapiens

<400> 118  
 Met Phe Ile Asn Ile Lys Ser Ile Leu Trp Met Cys Ser Thr Leu Ile  
 1 5 10 15  
 Val Thr His Ala Leu His Lys Val Lys Val Gly Lys Ser Pro Pro Val  
 20 25 30  
 Arg Gly Ser Leu Ser Gly Lys Val Ser Leu Pro Cys His Phe Ser Thr  
 35 40 45  
 Met Pro Thr Leu Pro Pro Ser Tyr Asn Thr Ser Glu Phe Leu Arg Ile  
 50 55 60  
 Lys Trp Ser Lys Ile Glu Val Asp Lys Asn Gly Lys Asp Leu Lys Glu  
 65 70 75 80  
 Thr Thr Val Leu Val Ala Gln Asn Gly Asn Ile Lys Ile Gly Gln Asp  
 85 90 95  
 Tyr Lys Gly Arg Val Ser Val Pro Thr His Pro Glu Ala Val Gly Asp  
 100 105 110  
 Ala Ser Leu Thr Val Val Lys Leu Leu Ala Ser Asp Ala Gly Leu Tyr  
 115 120 125  
 Arg Cys Asp Val Met Tyr Gly Ile Glu Asp Thr Gln Asp Thr Val Ser  
 130 135 140  
 Leu Thr Val Asp Gly Val Val Phe His Tyr Arg Ala Ala Thr Ser Arg  
 145 150 155 160  
 Tyr Thr Leu Asn Phe Glu Ala Ala Gln Lys Ala Cys Leu Asp Val Gly  
 165 170 175  
 Ala Val Ile Ala Thr Pro Glu Gln Leu Phe Ala Ala Tyr Glu Asp Gly  
 180 185 190  
 Phe Glu Gln Cys Asp Ala Gly Trp Leu Ala Asp Gln Thr Val Arg Tyr  
 195 200 205  
 Pro Ile Arg Ala Pro Arg Val Gly Cys Tyr Gly Asp Lys Met Gly Lys  
 210 215 220  
 Ala Gly Val Arg Thr Tyr Gly Phe Arg Ser Pro Gln Glu Thr Tyr Asp  
 225 230 235 240  
 Val Tyr Cys Tyr Val Asp His Leu Asp Gly Asp Val Phe His Leu Thr  
 245 250 255  
 Val Pro Ser Lys Phe Thr Phe Glu Glu Ala Ala Lys Glu Cys Glu Asn  
 260 265 270  
 Gln Asp Ala Arg Leu Ala Thr Val Gly Glu Leu Gln Ala Ala Trp Arg  
 275 280 285  
 Asn Gly Phe Asp Gln Cys Asp Tyr Gly Trp Leu Ser Asp Ala Ser Val  
 290 295 300  
 Arg His Pro Val Thr Val Ala Arg Ala Gln Cys Gly Gly Gly Leu Leu  
 305 310 315 320  
 Gly Val Arg Thr Leu Tyr Arg Phe Glu Asn Gln Thr Gly Phe Pro Pro  
 325 330 335  
 Pro Asp Ser Arg Phe Asp Ala Tyr Cys Phe Lys Pro Lys Glu Ala Thr  
 340 345 350  
 Thr Ile Asp Leu Ser Ile Leu Ala Glu Thr Ala Ser Pro Ser Leu Ser  
 355 360 365  
 Lys Glu Pro Gln Met Val Ser Asp Arg Thr Thr Pro Ile Ile Pro Leu  
 370 375 380  
 Val Asp Glu Leu Pro Val Ile Pro Thr Glu Phe Pro Pro Val Gly Asn  
 385 390 395 400  
 Ile Val Ser Phe Glu Gln Lys Ala Thr Val Gln Pro Gln Ala Ile Thr  
 405 410 415  
 Asp Ser Leu Ala Thr Lys Leu Pro Thr Pro Thr Gly Ser Thr Lys Lys  
 420 425 430  
 Pro Trp Asp Met Asp Asp Tyr Ser Pro Ser Ala Ser Gly Pro Leu Gly

## SEQUENCE LISTING 1657-2022.txt

435  
 Lys Leu Asp Ile Ser Glu Ile Lys Glu Glu Val Leu Gln Ser Thr Thr  
 450  
 Gly Val Ser His Tyr Ala Thr Asp Ser Trp Asp Gly Val Val Glu Asp  
 465  
 Lys Gln Thr Gln Glu Ser Val Thr Gln Ile Glu Gln Ile Glu Val Gly  
 485  
 Pro Leu Val Thr Ser Met Glu Ile Leu Lys His Ile Pro Ser Lys Glu  
 500  
 Phe Pro Val Thr Glu Thr Pro Leu Val Thr Ala Arg Met Ile Leu Glu  
 515  
 Ser Lys Thr Glu Lys Lys Met Val Ser Thr Val Ser Glu Leu Val Thr  
 530  
 Thr Gly His Tyr Gly Phe Thr Leu Gly Glu Glu Asp Asp Glu Asp Arg  
 545  
 Thr Leu Thr Val Gly Ser Asp Glu Ser Thr Leu Ile Phe Asp Gln Ile  
 565  
 Pro Glu Val Ile Thr Val Ser Lys Thr Ser Glu Asp Thr Ile His Thr  
 580  
 His Leu Glu Asp Leu Glu Ser Val Ser Ala Ser Thr Thr Val Ser Pro  
 595  
 Leu Ile Met Pro Asp Asn Asn Gly Ser Ser Met Asp Asp Trp Glu Glu  
 610  
 Arg Gln Thr Ser Gly Arg Ile Thr Glu Glu Phe Leu Gly Lys Tyr Leu  
 625  
 Ser Thr Thr Pro Phe Pro Ser Gln His Arg Thr Glu Ile Glu Leu Phe  
 645  
 Pro Tyr Ser Gly Asp Lys Ile Leu Val Glu Gly Ile Ser Thr Val Ile  
 660  
 Tyr Pro Ser Leu Gln Thr Glu Met Thr His Arg Arg Glu Arg Thr Glu  
 675  
 Thr Leu Ile Pro Glu Met Arg Thr Asp Thr Tyr Thr Asp Glu Ile Gln  
 690  
 Glu Glu Ile Thr Lys Ser Pro Phe Met Gly Lys Thr Glu Glu Glu Val  
 705  
 Phe Ser Gly Met Lys Leu Ser Thr Ser Leu Ser Glu Pro Ile His Val  
 725  
 Thr Glu Ser Ser Val Glu Met Thr Lys Ser Phe Asp Phe Pro Thr Leu  
 740  
 Ile Thr Lys Leu Ser Ala Glu Pro Thr Glu Val Arg Asp Met Glu Glu  
 755  
 Asp Phe Thr Ala Thr Pro Gly Thr Thr Lys Tyr Asp Glu Asn Ile Thr  
 770  
 Thr Val Leu Leu Ala His Gly Thr Leu Ser Val Glu Ala Ala Thr Val  
 785  
 Ser Lys Trp Ser Trp Asp Glu Asp Asn Thr Thr Ser Lys Pro Leu Glu  
 805  
 Ser Thr Glu Pro Ser Ala Ser Ser Lys Leu Pro Pro Ala Leu Leu Thr  
 820  
 Thr Val Gly Met Asn Gly Lys Asp Lys Asp Ile Pro Ser Phe Thr Glu  
 835  
 Asp Gly Ala Asp Glu Phe Thr Leu Ile Pro Asp Ser Thr Gln Lys Gln  
 850  
 Leu Glu Glu Val Thr Asp Glu Asp Ile Ala Ala His Gly Lys Phe Thr  
 865  
 Ile Arg Phe Gln Pro Thr Thr Ser Thr Gly Ile Ala Glu Lys Ser Thr  
 885  
 Leu Arg Asp Ser Thr Thr Glu Glu Lys Val Pro Pro Ile Thr Ser Thr  
 900  
 Glu Gly Gln Val Tyr Ala Thr Met Glu Gly Ser Ala Leu Gly Glu Val  
 915  
 Glu Asp Val Asp Leu Ser Lys Pro Val Ser Thr Val Pro Gln Phe Ala  
 930  
 His Thr Ser Glu Val Glu Gly Leu Ala Phe Val Ser Tyr Ser Ser Thr  
 945  
 Gln Glu Pro Thr Thr Tyr Val Asp Ser Ser His Thr Ile Pro Leu Ser  
 965  
 970  
 975

## SEQUENCE LISTING 1657-2022.txt

val Ile Pro Lys Thr Asp Trp Gly Val Leu Val Pro Ser Val Pro Ser  
 980 985 990  
 Glu Asp Glu Val Leu Gly Glu Pro Ser Gln Asp Ile Leu Val Ile Asp  
 995 1000 1005  
 Gln Thr Arg Leu Glu Ala Thr Ile Ser Pro Glu Thr Met Arg Thr Thr  
 1010 1015 1020  
 Lys Ile Thr Glu Gly Thr Thr Gln Glu Glu Phe Pro Trp Lys Glu Gln  
 1025 1030 1035 1040  
 Thr Ala Glu Lys Pro Val Pro Ala Leu Ser Ser Thr Ala Trp Thr Pro  
 1045 1050 1055  
 Lys Glu Ala Val Thr Pro Leu Asp Glu Gln Glu Gly Asp Gly Ser Ala  
 1060 1065 1070  
 Tyr Thr Val Ser Glu Asp Glu Leu Thr Gly Ser Glu Arg Val Pro  
 1075 1080 1085  
 Val Leu Glu Thr Thr Pro Val Gly Lys Ile Asp His Ser Val Ser Tyr  
 1090 1095 1100  
 Pro Pro Gly Ala Val Thr Glu His Lys Val Lys Thr Asp Glu Val Val  
 1105 1110 1115 1120  
 Thr Leu Thr Pro Arg Ile Gly Pro Lys Val Ser Leu Ser Pro Gly Pro  
 1125 1130 1135  
 Glu Gln Lys Tyr Glu Thr Glu Gly Ser Ser Thr Thr Gly Phe Thr Ser  
 1140 1145 1150  
 Ser Leu Ser Pro Phe Ser Thr His Ile Thr Gln Leu Met Glu Glu Thr  
 1155 1160 1165  
 Thr Thr Glu Lys Thr Ser Leu Glu Asp Ile Asp Leu Gly Ser Gly Leu  
 1170 1175 1180  
 Phe Glu Lys Pro Lys Ala Thr Glu Leu Ile Glu Phe Ser Thr Ile Lys  
 1185 1190 1195 1200  
 Val Thr Val Pro Ser Asp Ile Thr Thr Ala Phe Ser Ser Val Asp Arg  
 1205 1210 1215  
 Leu His Thr Thr Ser Ala Phe Lys Pro Ser Ser Ala Ile Thr Lys Lys  
 1220 1225 1230  
 Pro Pro Leu Ile Asp Arg Glu Pro Gly Glu Glu Thr Thr Ser Asp Met  
 1235 1240 1245  
 Val Ile Ile Gly Glu Ser Thr Ser His Val Pro Pro Thr Thr Leu Glu  
 1250 1255 1260  
 Asp Ile Val Ala Lys Glu Thr Glu Thr Asp Ile Asp Arg Glu Tyr Phe  
 1265 1270 1275 1280  
 Thr Thr Ser Ser Pro Pro Ala Thr Gln Pro Thr Arg Pro Pro Thr Val  
 1285 1290 1295  
 Glu Asp Lys Glu Ala Phe Gly Pro Gln Ala Leu Ser Thr Pro Gln Pro  
 1300 1305 1310  
 Pro Ala Ser Thr Lys Phe His Pro Asp Ile Asn Val Tyr Ile Ile Glu  
 1315 1320 1325  
 Val Arg Glu Asn Lys Thr Gly Arg Met Ser Asp Leu Ser Val Ile Gly  
 1330 1335 1340  
 His Pro Ile Asp Ser Glu Ser Lys Glu Asp Glu Pro Cys Ser Glu Glu  
 1345 1350 1355 1360  
 Thr Asp Pro Val His Asp Leu Met Ala Glu Ile Leu Pro Glu Phe Pro  
 1365 1370 1375  
 Asp Ile Ile Glu Ile Asp Leu Tyr His Ser Glu Glu Asn Glu Glu Glu  
 1380 1385 1390  
 Glu Glu Glu Cys Ala Asn Ala Thr Asp Val Thr Thr Thr Pro Ser Val  
 1395 1400 1405  
 Gln Tyr Ile Asn Gly Lys His Leu Val Thr Thr Val Pro Lys Asp Pro  
 1410 1415 1420  
 Glu Ala Ala Glu Ala Arg Arg Gly Gln Phe Glu Ser Val Ala Pro Ser  
 1425 1430 1435 1440  
 Gln Asn Phe Ser Asp Ser Ser Glu Ser Asp Thr His Pro Phe Val Ile  
 1445 1450 1455  
 Ala Lys Thr Glu Leu Ser Thr Ala Val Gln Pro Asn Glu Ser Thr Glu  
 1460 1465 1470  
 Thr Thr Glu Ser Leu Glu Val Thr Trp Lys Pro Glu Thr Tyr Pro Glu  
 1475 1480 1485  
 Thr Ser Glu His Phe Ser Gly Gly Glu Pro Asp Val Phe Pro Thr Val  
 1490 1495 1500  
 Pro Phe His Glu Glu Phe Glu Ser Gly Thr Ala Lys Lys Gly Ala Glu

## SEQUENCE LISTING 1657-2022.txt

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1505          1510          1515          1520
Ser Val Thr Glu Arg Asp Thr Glu Val Gly His Gln Ala His Glu His
1525          1530          1535
Thr Glu Pro Val Ser Leu Phe Pro Glu Ser Ser Gly Glu Ile Ala
1540          1545          1550
Ile Asp Gln Glu Ser Gln Lys Ile Ala Phe Ala Arg Ala Thr Glu Val
1555          1560          1565
Thr Phe Gly Glu Glu Val Glu Lys Ser Thr Ser Val Thr Tyr Thr Pro
1570          1575          1580
Thr Ile Val Pro Ser Ser Ala Ser Ala Tyr Val Ser Glu Glu Glu Ala
1585          1590          1595          1600
Val Thr Leu Ile Gly Asn Pro Trp Pro Asp Leu Leu Ser Thr Lys
1605          1610          1615
Glu Ser Trp Val Glu Ala Thr Pro Arg Gln Val Val Glu Leu Ser Gly
1620          1625          1630
Ser Ser Ser Ile Pro Ile Thr Glu Gly Ser Gly Glu Ala Glu Glu Asp
1635          1640          1645
Glu Asp Thr Met Phe Thr Met Val Thr Asp Leu Ser Gln Arg Asn Thr
1650          1655          1660
Thr Asp Thr Leu Ile Thr Leu Asp Thr Ser Arg Ile Ile Thr Glu Ser
1665          1670          1675          1680
Phe Phe Glu Val Pro Ala Thr Thr Ile Tyr Pro Val Ser Glu Gln Pro
1685          1690          1695
Ser Ala Lys Val Val Pro Thr Lys Phe Val Ser Glu Thr Asp Thr Ser
1700          1705          1710
Glu Trp Ile Ser Ser Thr Thr Val Glu Glu Lys Lys Arg Lys Glu Glu
1715          1720          1725
Glu Gly Thr Thr Gly Thr Ala Ser Thr Phe Glu Val Tyr Ser Ser Thr
1730          1735          1740
Gln Arg Ser Asp Gln Leu Ile Leu Pro Phe Glu Leu Glu Ser Pro Asn
1745          1750          1755          1760
Val Ala Thr Ser Ser Asp Ser Gly Thr Arg Lys Ser Phe Met Ser Leu
1765          1770          1775
Thr Thr Pro Thr Gln Ser Glu Arg Glu Met Thr Asp Ser Thr Pro Val
1780          1785          1790
Phe Thr Glu Thr Asn Thr Leu Glu Asn Leu Gly Ala Gln Thr Thr Glu
1795          1800          1805
His Ser Ser Ile His Gln Pro Gly Val Gln Glu Gly Leu Thr Thr Leu
1810          1815          1820
Pro Arg Ser Pro Ala Ser Val Phe Met Glu Gln Gly Ser Gly Glu Ala
1825          1830          1835          1840
Ala Ala Asp Pro Glu Thr Thr Thr Val Ser Ser Phe Ser Leu Asn Val
1845          1850          1855
Glu Tyr Ala Ile Gln Ala Glu Lys Glu Val Ala Gly Thr Leu Ser Pro
1860          1865          1870
His Val Glu Thr Thr Phe Ser Thr Glu Pro Thr Gly Leu Val Leu Ser
1875          1880          1885
Thr Val Met Asp Arg Val Val Ala Glu Asn Ile Thr Gln Thr Ser Arg
1890          1895          1900
Glu Ile Val Ile Ser Glu Arg Leu Gly Glu Pro Asn Tyr Gly Ala Glu
1905          1910          1915          1920
Ile Arg Gly Phe Ser Thr Gly Phe Pro Leu Glu Glu Asp Phe Ser Gly
1925          1930          1935
Asp Phe Arg Glu Tyr Ser Thr Val Ser His Pro Ile Ala Lys Glu Glu
1940          1945          1950
Thr Val Met Met Glu Gly Ser Gly Asp Ala Ala Phe Arg Asp Thr Gln
1955          1960          1965
Thr Ser Pro Ser Thr Val Pro Thr Ser Val His Ile Ser His Ile Ser
1970          1975          1980
Asp Ser Glu Gly Pro Ser Thr Met Val Ser Thr Ser Ala Phe Pro
1985          1990          1995          2000
Trp Glu Glu Phe Thr Ser Ser Ala Glu Gly Ser Gly Glu Gln Leu Val
2005          2010          2015
Thr Val Ser Ser Val Val Pro Val Leu Pro Ser Ala Val Gln Lys
2020          2025          2030
Phe Ser Gly Thr Ala Ser Ser Ile Ile Asp Glu Gly Leu Gly Glu Val
2035          2040          2045

```



## SEQUENCE LISTING 1657-2022.txt

Gly Thr Val Asn Glu Ile Asp Arg Arg Ser Thr Ile Leu Pro Thr Ala  
 2050 2055 2060  
 Glu Val Glu Gly Thr Lys Ala Pro Val Glu Lys Glu Glu Val Lys Val  
 2065 2070 2075 2080  
 Ser Gly Thr Val Ser Thr Asn Phe Pro Gln Thr Ile Glu Pro Ala Lys  
 2085 2090 2095  
 Leu Trp Ser Arg Gln Glu Val Asn Pro Val Arg Gln Glu Ile Glu Ser  
 2100 2105 2110  
 Glu Thr Thr Ser Glu Glu Gln Ile Gln Glu Glu Lys Ser Phe Glu Ser  
 2115 2120 2125  
 Pro Gln Asn Ser Pro Ala Thr Glu Gln Thr Ile Phe Asp Ser Gln Thr  
 2130 2135 2140  
 Phe Thr Glu Thr Glu Leu Lys Thr Thr Asp Tyr Ser Val Leu Thr Thr  
 2145 2150 2155 2160  
 Lys Lys Thr Tyr Ser Asp Asp Lys Glu Met Lys Glu Glu Asp Thr Ser  
 2165 2170 2175  
 Leu Val Asn Met Ser Thr Pro Asp Pro Asp Ala Asn Gly Leu Glu Ser  
 2180 2185 2190  
 Tyr Thr Thr Leu Pro Glu Ala Thr Glu Lys Ser His Phe Phe Leu Ala  
 2195 2200 2205  
 Thr Ala Leu Val Thr Glu Ser Ile Pro Ala Glu His Val Val Thr Asp  
 2210 2215 2220  
 Ser Pro Ile Lys Lys Glu Glu Ser Thr Lys His Phe Pro Lys Gly Met  
 2225 2230 2235 2240  
 Arg Pro Thr Ile Gln Glu Ser Asp Thr Glu Leu Leu Phe Ser Gly Leu  
 2245 2250 2255  
 Gly Ser Gly Glu Glu Val Leu Pro Thr Leu Pro Thr Glu Ser Val Asn  
 2260 2265 2270  
 Phe Thr Glu Val Glu Gln Ile Asn Asn Thr Leu Tyr Pro His Thr Ser  
 2275 2280 2285  
 Gln Val Glu Ser Thr Ser Ser Asp Lys Ile Glu Asp Phe Asn Arg Met  
 2290 2295 2300  
 Glu Asn Val Ala Lys Glu Val Gly Pro Leu Val Ser Gln Thr Asp Ile  
 2305 2310 2315 2320  
 Phe Glu Gly Ser Gly Ser Val Thr Ser Thr Thr Leu Ile Glu Ile Leu  
 2325 2330 2335  
 Ser Asp Thr Gly Ala Glu Gly Pro Thr Val Ala Pro Leu Pro Phe Ser  
 2340 2345 2350  
 Thr Asp Ile Gly His Pro Gln Asn Gln Thr Val Arg Trp Ala Glu Glu  
 2355 2360 2365  
 Ile Gln Thr Ser Arg Pro Gln Thr Ile Thr Glu Gln Asp Ser Asn Lys  
 2370 2375 2380  
 Asn Ser Ser Thr Ala Glu Ile Asn Glu Thr Thr Thr Ser Ser Thr Asp  
 2385 2390 2395 2400  
 Phe Leu Ala Arg Ala Tyr Gly Phe Glu Met Ala Lys Glu Phe Val Thr  
 2405 2410 2415  
 Ser Ala Pro Lys Pro Ser Asp Leu Tyr Tyr Glu Pro Ser Gly Glu Gly  
 2420 2425 2430  
 Ser Gly Glu Val Asp Ile Val Asp Ser Phe His Thr Ser Ala Thr Thr  
 2435 2440 2445  
 Gln Ala Thr Arg Gln Glu Ser Ser Thr Thr Phe Val Ser Asp Gly Ser  
 2450 2455 2460  
 Leu Glu Lys His Pro Glu Val Pro Ser Ala Lys Ala Val Thr Ala Asp  
 2465 2470 2475 2480  
 Gly Phe Pro Thr Val Ser Val Met Leu Pro Leu His Ser Glu Gln Asn  
 2485 2490 2495  
 Lys Ser Ser Pro Asp Pro Thr Ser Thr Leu Ser Asn Thr Val Ser Tyr  
 2500 2505 2510  
 Glu Arg Ser Thr Asp Gly Ser Phe Gln Asp Arg Phe Arg Glu Phe Glu  
 2515 2520 2525  
 Asp Ser Thr Leu Lys Pro Asn Arg Lys Lys Pro Thr Glu Asn Ile Ile  
 2530 2535 2540  
 Ile Asp Leu Asp Lys Glu Asp Lys Asp Leu Ile Leu Thr Ile Thr Glu  
 2545 2550 2555 2560  
 Ser Thr Ile Leu Glu Ile Leu Pro Glu Leu Thr Ser Asp Lys Asn Thr  
 2565 2570 2575  
 Ile Ile Asp Ile Asp His Thr Lys Pro Val Tyr Glu Asp Ile Leu Gly

## SEQUENCE LISTING 1657-2022.txt

2580 Met Gln Thr Asp Ile Asp Thr Glu Val Pro Ser Glu Pro His Asp Ser  
 2585 2590  
 2595 Asn Asp Glu Ser Asn Asp Asp Ser Thr Gln Val Gln Glu Ile Tyr Glu  
 2600 2605  
 2610 Ala Ala Val Asn Leu Ser Leu Thr Glu Glu Thr Phe Glu Gly Ser Ala  
 2615 2620  
 2625 Asp Val Leu Ala Ser Tyr Thr Gln Ala Thr His Asp Glu Ser Met Thr  
 2630 2635  
 2645 Tyr Glu Asp Arg Ser Gln Leu Asp His Met Gly Phe His Phe Thr Thr  
 2650 2655  
 2660 Gly Ile Pro Ala Pro Ser Thr Glu Thr Glu Leu Asp Val Leu Leu Pro  
 2665 2670  
 2675 Thr Ala Thr Ser Leu Pro Ile Pro Arg Lys Ser Ala Thr Val Ile Pro  
 2680 2685  
 2690 Glu Ile Glu Gly Ile Lys Ala Glu Ala Lys Ala Leu Asp Asp Met Phe  
 2695 2700  
 2705 Glu Ser Ser Thr Leu Ser Asp Gly Gln Ala Ile Ala Asp Gln Ser Glu  
 2710 2715  
 2725 Ile Ile Pro Thr Leu Gly Gln Phe Glu Arg Thr Gln Glu Glu Tyr Glu  
 2730 2735  
 2740 Asp Lys Lys His Ala Gly Pro Ser Phe Gln Pro Glu Phe Ser Ser Gly  
 2745 2750  
 2755 Ala Glu Glu Ala Leu Val Asp His Thr Pro Tyr Leu Ser Ile Ala Thr  
 2760 2765  
 2770 Thr His Leu Met Asp Gln Ser Val Thr Glu Val Pro Asp Val Met Glu  
 2775 2780  
 2785 Gly Ser Asn Pro Pro Tyr Tyr Thr Asp Thr Thr Leu Ala Val Ser Thr  
 2790 2795  
 2805 Phe Ala Lys Leu Ser Ser Gln Thr Pro Ser Ser Pro Leu Thr Ile Tyr  
 2810 2815  
 2820 Ser Gly Ser Glu Ala Ser Gly His Thr Glu Ile Pro Gln Pro Ser Ala  
 2825 2830  
 2835 Leu Pro Gly Ile Asp Val Gly Ser Ser Val Met Ser Pro Gln Asp Ser  
 2840 2845  
 2850 Phe Lys Glu Ile His Val Asn Ile Glu Ala Thr Phe Lys Pro Ser Ser  
 2855 2860  
 2865 Glu Glu Tyr Leu His Ile Thr Glu Pro Pro Ser Leu Ser Pro Asp Thr  
 2870 2875  
 2885 Lys Leu Glu Pro Ser Glu Asp Asp Gly Lys Pro Glu Leu Leu Glu Glu  
 2890 2895  
 2900 Met Glu Ala Ser Pro Thr Glu Leu Ile Ala Val Glu Gly Thr Glu Ile  
 2905 2910  
 2915 Leu Gln Asp Phe Gln Asn Lys Thr Asp Gly Gln Val Ser Gly Glu Ala  
 2920 2925  
 2930 Ile Lys Met Phe Pro Thr Ile Lys Thr Pro Glu Ala Gly Thr Val Ile  
 2935 2940  
 2945 Thr Thr Ala Asp Glu Ile Glu Leu Glu Gly Ala Thr Gln Trp Pro His  
 2950 2955  
 2965 Ser Thr Ser Ala Ser Ala Thr Tyr Gly Val Glu Ala Gly Val Val Pro  
 2970 2975  
 2980 Trp Leu Ser Pro Gln Thr Ser Glu Arg Pro Thr Leu Ser Ser Ser Pro  
 2985 2990  
 2995 Glu Ile Asn Pro Glu Thr Gln Ala Ala Leu Ile Arg Gly Gln Asp Ser  
 3000 3005  
 3010 Thr Ile Ala Ala Ser Glu Gln Gln Val Ala Ala Arg Ile Leu Asp Ser  
 3015 3020  
 3025 Asn Asp Gln Ala Thr Val Asn Pro Val Glu Phe Asn Thr Glu Val Ala  
 3030 3035  
 3045 Thr Pro Pro Phe Ser Leu Leu Glu Thr Ser Asn Glu Thr Asp Phe Leu  
 3050 3055  
 3060 Ile Gly Ile Asn Glu Glu Ser Val Glu Gly Thr Ala Ile Tyr Leu Pro  
 3065 3070  
 3075 Gly Pro Asp Arg Cys Lys Met Asn Pro Cys Leu Asn Gly Gly Thr Cys  
 3080 3085  
 3090 Tyr Pro Thr Glu Thr Ser Tyr Val Cys Thr Cys Val Pro Gly Tyr Ser  
 3095 3100  
 3105 3110 3115 3120

## SEQUENCE LISTING 1657-2022.txt

Gly Asp Gln Cys Glu Leu Asp Phe Asp Glu Cys His Ser Asn Pro Cys  
 3125 3130 3135  
 Arg Asn Gly Ala Thr Cys Val Asp Gly Phe Asn Thr Phe Arg Cys Leu  
 3140 3145 3150  
 Cys Leu Pro Ser Tyr Val Gly Ala Leu Cys Glu Gln Asp Thr Glu Thr  
 3155 3160 3165  
 Cys Asp Tyr Gly Trp His Lys Phe Gln Gly Gln Cys Tyr Lys Tyr Phe  
 3170 3175 3180  
 Ala His Arg Arg Thr Trp Asp Ala Ala Glu Arg Glu Cys Arg Leu Gln  
 3185 3190 3195 3200  
 Gly Ala His Leu Thr Ser Ile Leu Ser His Glu Glu Gln Met Phe Val  
 3205 3210 3215  
 Asn Arg Val Gly His Asp Tyr Gln Trp Ile Gly Leu Asn Asp Lys Met  
 3220 3225 3230  
 Phe Glu His Asp Phe Arg Trp Thr Asp Gly Ser Thr Leu Gln Tyr Glu  
 3235 3240 3245  
 Asn Trp Arg Pro Asn Gln Pro Asp Ser Phe Phe Ser Ala Gly Glu Asp  
 3250 3255 3260  
 Cys Val Val Ile Ile Trp His Glu Asn Gly Gln Trp Asn Asp Val Pro  
 3265 3270 3275 3280  
 Cys Asn Tyr His Leu Thr Tyr Thr Cys Lys Lys Gly Thr Val Ala Cys  
 3285 3290 3295  
 Gly Gln Pro Pro Val Val Glu Asn Ala Lys Thr Phe Gly Lys Met Lys  
 3300 3305 3310  
 Pro Arg Tyr Glu Ile Asn Ser Leu Ile Arg Tyr His Cys Lys Asp Gly  
 3315 3320 3325  
 Phe Ile Gln Arg His Leu Pro Thr Ile Arg Cys Leu Gly Asn Gly Arg  
 3330 3335 3340  
 Trp Ala Ile Pro Lys Ile Thr Cys Met Asn Pro Ser Ala Tyr Gln Arg  
 3345 3350 3355 3360  
 Thr Tyr Ser Met Lys Tyr Phe Lys Asn Ser Ser Ser Ala Lys Asp Asn  
 3365 3370 3375  
 Ser Ile Asn Thr Ser Lys His Asp His Arg Trp Ser Arg Arg Trp Gln  
 3380 3385 3390  
 Glu Ser Arg Arg  
 3395

<210> 119  
 <211> 317  
 <212> PRT  
 <213> Homo sapiens

<400> 119  
 Met Thr Ser Arg Thr Arg Val Thr Trp Pro Ser Pro Pro Arg Pro Leu  
 1 5 10 15  
 Pro Val Pro Ala Ala Ala Ala Val Ala Phe Gly Ala Lys Gly Thr Asp  
 20 25 30  
 Pro Ala Glu Ala Arg Ser Ser Arg Gly Ile Glu Glu Ala Gly Pro Arg  
 35 40 45  
 Ala His Gly Arg Ala Gly Arg Glu Pro Glu Arg Arg Arg Ser Arg Gln  
 50 55 60  
 Gln Arg Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr  
 65 70 75 80  
 Cys Ala Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala  
 85 90 95  
 Pro Trp Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val  
 100 105 110  
 Arg Thr Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala  
 115 120 125  
 Val Val Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr  
 130 135 140  
 Asn Phe Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp  
 145 150 155 160  
 Ala Asn Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile  
 165 170 175  
 Cys Ala Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile

## SEQUENCE LISTING 1657-2022.txt

```

180      185      190
Ile Pro Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu
195      200      205
Val Ala Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile
210      215      220
Arg Gln Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val
225      230      235
Asn Pro Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile
245      250      255
Leu Thr Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg
260      265      270
Tyr Ile Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser
275      280      285
Asn Asp Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn
290      295      300
Gly Ala Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala
305      310      315

```

```

<210> 120
<211> 474
<212> PRT
<213> Homo sapiens

```

```

<400> 120
Met Val Gln Gln Thr Asn Asn Ala Glu Asn Thr Glu Ala Leu Leu Ala
1      5      10      15
Gly Glu Ser Ser Asp Ser Gly Ala Gly Leu Glu Leu Gly Ile Ala Ser
20      25      30
Ser Pro Thr Pro Gly Ser Thr Ala Ser Thr Gly Gly Lys Ala Asp Asp
35      40      45
Pro Ser Trp Cys Lys Thr Pro Ser Gly His Ile Lys Arg Pro Met Asn
50      55      60
Ala Phe Met Val Trp Ser Gln Ile Glu Arg Arg Lys Ile Met Glu Gln
65      70      75      80
Ser Pro Asp Met His Asn Ala Glu Ile Ser Lys Arg Leu Gly Lys Arg
85      90      95
Trp Lys Leu Leu Lys Asp Ser Asp Lys Ile Pro Phe Ile Arg Glu Ala
100      105      110
Glu Arg Leu Arg Leu Lys His Met Ala Asp Tyr Pro Asp Tyr Lys Tyr
115      120      125
Arg Pro Arg Lys Lys Val Lys Ser Gly Asn Ala Asn Ser Ser Ser Ser
130      135      140
Ala Ala Ala Ser Ser Lys Pro Gly Glu Lys Gly Asp Lys Val Gly Gly
145      150      155      160
Ser Gly Gly Gly Gly His Gly Gly Gly Gly Gly Gly Ser Ser Asn
165      170      175
Ala Gly Gly Gly Gly Gly Gly Ala Ser Gly Gly Gly Ala Asn Ser Lys
180      185      190
Pro Ala Gln Lys Lys Ser Cys Gly Ser Lys Val Ala Gly Gly Ala Gly
195      200      205
Gly Gly Val Ser Lys Pro His Ala Lys Leu Ile Leu Ala Gly Gly Gly
210      215      220
Gly Gly Gly Lys Ala Ala Ala Ala Ala Ser Phe Ala Ala Glu
225      230      235
Gln Ala Gly Ala Ala Ala Leu Leu Pro Leu Gly Ala Ala Ala Asp His
245      250      255
His Ser Leu Tyr Lys Ala Arg Thr Pro Ser Ala Ser Ala Ser
260      265      270
Ser Ala Ala Ser Ala Ser Ala Ala Leu Ala Ala Pro Gly Lys His Leu
275      280      285
Ala Glu Lys Lys Val Lys Arg Val Tyr Leu Phe Gly Gly Leu Gly Thr
290      295      300
Ser Ser Ser Pro Val Gly Gly Val Gly Ala Gly Ala Asp Pro Ser Asp
305      310      315
Pro Leu Gly Leu Tyr Glu Glu Glu Gly Ala Gly Cys Ser Pro Asp Ala
325      330      335

```

## SEQUENCE LISTING 1657-2022.txt

Pro Ser Leu Ser Gly Arg Ser Ser Ala Ala Ser Ser Pro Ala Ala Gly  
 340 345 350  
 Arg Ser Pro Ala Asp His Arg Gly Tyr Ala Ser Leu Arg Ala Ala Ser  
 355 360 365  
 Pro Ala Pro Ser Ser Ala Pro Ser His Ala Ser Ser Ala Ser Ser  
 370 375 380  
 His Ser Ser Ser Ser Ser Ser Ser Gly Ser Ser Ser Ser Asp Asp Glu  
 385 390 395 400  
 Phe Glu Asp Asp Leu Asp Leu Asn Pro Ser Ser Asn Phe Glu Ser  
 405 410 415  
 Met Ser Leu Gly Ser Phe Ser Ser Ser Ser Ala Leu Asp Arg Asp Leu  
 420 425 430  
 Asp Phe Asn Phe Glu Pro Gly Ser Gly Ser His Phe Glu Phe Pro Asp  
 435 440 445  
 Tyr Cys Thr Pro Glu Val Ser Glu Met Ile Ser Gly Asp Trp Leu Glu  
 450 455 460  
 Ser Ser Ile Ser Asn Leu Val Phe Thr Tyr  
 465 470

<210> 121  
 <211> 357  
 <212> PRT  
 <213> Homo sapiens

<400> 121  
 Met Ala Ala Ala Ala Lys Pro Asn Asn Leu Ser Leu Val Val His Gly  
 1 5 10 15  
 Pro Gly Asp Leu Arg Leu Glu Asn Tyr Pro Ile Pro Glu Pro Gly Pro  
 20 25 30  
 Asn Glu Val Leu Leu Arg Met His Ser Val Gly Ile Cys Gly Ser Asp  
 35 40 45  
 Val His Tyr Trp Glu Tyr Gly Arg Ile Gly Asn Phe Ile Val Lys Lys  
 50 55 60  
 Pro Met Val Leu Gly His Glu Ala Ser Gly Thr Val Glu Lys Val Gly  
 65 70 75 80  
 Ser Ser Val Lys His Leu Lys Pro Gly Asp Arg Val Ala Ile Glu Pro  
 85 90 95  
 Gly Ala Pro Arg Glu Asn Asp Glu Phe Cys Lys Met Gly Arg Tyr Asn  
 100 105 110  
 Leu Ser Pro Ser Ile Phe Phe Cys Ala Thr Pro Pro Asp Asp Gly Asn  
 115 120 125  
 Leu Cys Arg Phe Tyr Lys His Asn Ala Ala Phe Cys Tyr Lys Leu Pro  
 130 135 140  
 Asp Asn Val Thr Phe Glu Glu Gly Ala Leu Ile Glu Pro Leu Ser Val  
 145 150 155 160  
 Gly Ile His Ala Cys Arg Arg Gly Gly Val Thr Leu Gly His Lys Val  
 165 170 175  
 Leu Val Cys Gly Ala Gly Pro Ile Gly Met Val Thr Leu Leu Val Ala  
 180 185 190  
 Lys Ala Met Gly Ala Ala Gln Val Val Val Thr Asp Leu Ser Ala Thr  
 195 200 205  
 Arg Leu Ser Lys Ala Lys Glu Ile Gly Ala Asp Leu Val Leu Gln Ile  
 210 215 220  
 Ser Lys Glu Ser Pro Gln Glu Ile Ala Arg Lys Val Glu Gly Gln Leu  
 225 230 235 240  
 Gly Cys Lys Pro Glu Val Thr Ile Glu Cys Thr Gly Ala Glu Ala Ser  
 245 250 255  
 Ile Gln Ala Gly Ile Tyr Ala Thr Arg Ser Gly Gly Thr Leu Val Leu  
 260 265 270  
 Val Gly Leu Gly Ser Glu Met Thr Thr Val Pro Leu Leu His Ala Ala  
 275 280 285  
 Ile Arg Glu Val Asp Ile Lys Gly Val Phe Arg Tyr Cys Asn Thr Trp  
 290 295 300  
 Pro Val Ala Ile Ser Met Leu Ala Ser Lys Ser Val Asn Val Lys Pro  
 305 310 315 320  
 Leu Val Thr His Arg Phe Pro Leu Glu Lys Ala Leu Glu Ala Phe Glu

## SEQUENCE LISTING 1657-2022.txt

Thr Phe Lys Lys Gly Leu Gly Leu Lys Ile Met Leu Lys Cys Asp Pro  
 Ser Asp Gln Asn Pro  
 325 330 335  
 340 345 350  
 355

<210> 122  
 <211> 470  
 <212> PRT  
 <213> Homo sapiens

<400> 122  
 Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala  
 1 5 10 15  
 Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe  
 20 25 30  
 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu  
 35 40 45  
 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile  
 50 55 60  
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp  
 65 70 75 80  
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His  
 100 105 110  
 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu  
 115 120 125  
 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val  
 130 135 140  
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu  
 145 150 155 160  
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly  
 165 170 175  
 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly  
 195 200 205  
 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu  
 210 215 220  
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr  
 225 230 235 240  
 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg  
 245 250 255  
 Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro  
 260 265 270  
 Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe  
 275 280 285  
 Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg  
 290 295 300  
 Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu  
 305 310 315 320  
 Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr  
 325 330 335  
 Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr  
 340 345 350  
 Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile  
 355 360 365  
 His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val  
 370 375 380  
 Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr  
 385 390 395 400  
 Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys  
 405 410 415  
 Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val  
 420 425 430

## SEQUENCE LISTING 1657-2022.txt

Phe Tyr Ser Lys Asn Lys Tyr Tyr Phe Phe Gln Gly Ser Asn Gln  
 435 440 445  
 Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser  
 450 455 460  
 Asn Ser Trp Phe Gly Cys  
 465 470

<210> 123  
 <211> 165  
 <212> PRT  
 <213> Homo sapiens

<400> 123  
 Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu  
 1 5 10 15  
 Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys  
 20 25 30  
 Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln  
 35 40 45  
 Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser  
 50 55 60  
 Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val  
 65 70 75 80  
 Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly  
 85 90 95  
 Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val  
 100 105 110  
 Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu  
 115 120 125  
 Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met  
 130 135 140  
 Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser  
 145 150 155 160  
 Tyr Cys Ile Gly Gly  
 165

<210> 124  
 <211> 2828  
 <212> PRT  
 <213> Homo sapiens

<400> 124  
 Met Pro Lys Arg Ala His Trp Gly Ala Leu Ser Val Val Leu Ile Leu  
 1 5 10 15  
 Leu Trp Gly His Pro Arg Val Ala Leu Ala Cys Pro His Pro Cys Ala  
 20 25 30  
 Cys Tyr Val Pro Ser Glu Val His Cys Thr Phe Arg Ser Leu Ala Ser  
 35 40 45  
 Val Pro Ala Gly Ile Ala Arg His Val Glu Arg Ile Asn Leu Gly Phe  
 50 55 60  
 Asn Ser Ile Gln Ala Leu Ser Glu Thr Ser Phe Ala Gly Leu Thr Lys  
 65 70 75 80  
 Leu Glu Leu Leu Met Ile His Gly Asn Glu Ile Pro Ser Ile Pro Asp  
 85 90 95  
 Gly Ala Leu Arg Asp Leu Ser Ser Leu Gln Val Phe Lys Phe Ser Tyr  
 100 105 110  
 Asn Lys Leu Arg Val Ile Thr Gly Gln Thr Leu Gln Gly Leu Ser Asn  
 115 120 125  
 Leu Met Arg Leu His Ile Asp His Asn Lys Ile Glu Phe Ile His Pro  
 130 135 140  
 Gln Ala Phe Asn Gly Leu Thr Ser Leu Arg Leu Leu His Leu Glu Gly  
 145 150 155 160  
 Asn Leu Leu His Gln Leu His Pro Ser Thr Phe Ser Thr Phe Thr Phe  
 165 170 175  
 Leu Asp Tyr Phe Arg Leu Ser Thr Ile Arg His Leu Tyr Leu Ala Glu

## SEQUENCE LISTING 1657-2022.txt

```

180
Asn Met Val Arg Thr Leu Pro Ala Ser Met Leu Arg Asn Met Pro Leu
195
Leu Glu Asn Leu Tyr Leu Gln Gly Asn Pro Trp Thr Cys Asp Cys Glu
210
Met Arg Trp Phe Leu Glu Trp Asp Ala Lys Ser Arg Gly Ile Leu Lys
225
Cys Lys Lys Asp Lys Ala Tyr Glu Gly Gly Gln Leu Cys Ala Met Cys
245
Phe Ser Pro Lys Lys Leu Tyr Lys His Glu Ile His Lys Leu Lys Asp
260
Met Thr Cys Leu Lys Pro Ser Ile Glu Ser Pro Leu Arg Gln Asn Arg
275
Ser Arg Ser Ile Glu Glu Glu Gln Glu Gln Glu Glu Asp Gly Gly Ser
290
Gln Leu Ile Leu Glu Lys Phe Gln Leu Pro Gln Trp Ser Ile Ser Leu
305
Asn Met Thr Asp Glu His Gly Asn Met Val Asn Leu Val Cys Asp Ile
325
Lys Lys Pro Met Asp Val Tyr Lys Ile His Leu Asn Gln Thr Asp Pro
340
Pro Asp Ile Asp Ile Asn Ala Thr Val Ala Leu Asp Phe Glu Cys Pro
355
Met Thr Arg Glu Asn Tyr Glu Lys Leu Trp Lys Leu Ile Ala Tyr Tyr
370
Ser Glu Val Pro Val Lys Leu His Arg Glu Leu Met Leu Ser Lys Asp
385
Pro Arg Val Ser Tyr Gln Tyr Arg Gln Asp Ala Asp Glu Glu Ala Leu
405
Tyr Tyr Thr Gly Val Arg Ala Gln Ile Leu Ala Glu Pro Glu Trp Val
420
Met Gln Pro Ser Ile Asp Ile Gln Leu Asn Arg Arg Gln Ser Thr Ala
435
Lys Lys Val Leu Leu Ser Tyr Tyr Thr Gln Tyr Ser Gln Thr Ile Ser
450
Thr Lys Asp Thr Arg Gln Ala Arg Gly Arg Ser Trp Val Met Ile Glu
465
Pro Ser Gly Ala Val Gln Arg Asp Gln Thr Val Leu Glu Gly Gly Pro
485
Cys Gln Leu Ser Cys Asn Val Lys Ala Ser Glu Ser Pro Ser Ile Phe
500
Trp Val Leu Pro Asp Gly Ser Ile Leu Lys Ala Pro Met Asp Asp Pro
515
Asp Ser Lys Phe Ser Ile Leu Ser Ser Gly Trp Leu Arg Ile Lys Ser
530
Met Glu Pro Ser Asp Ser Gly Leu Tyr Gln Cys Ile Ala Gln Val Arg
545
Asp Glu Met Asp Arg Met Val Tyr Arg Val Leu Val Gln Ser Pro Ser
565
Thr Gln Pro Ala Glu Lys Asp Thr Val Thr Ile Gly Lys Asn Pro Gly
580
Glu Ser Val Thr Leu Pro Cys Asn Ala Leu Ala Ile Pro Glu Ala His
595
Leu Ser Trp Ile Leu Pro Asn Arg Arg Ile Ile Asn Asp Leu Ala Asn
610
Thr Ser His Val Tyr Met Leu Pro Asn Gly Thr Leu Ser Ile Pro Lys
625
Val Gln Val Ser Asp Ser Gly Tyr Tyr Arg Cys Val Ala Val Asn Gln
645
Gln Gly Ala Asp His Phe Thr Val Gly Ile Thr Val Thr Lys Lys Gly
660
Ser Gly Leu Pro Ser Lys Arg Gly Arg Arg Pro Gly Ala Lys Ala Leu
675
Ser Arg Val Arg Glu Asp Ile Val Glu Asp Glu Gly Ser Gly Met
690
Gly Asp Glu Glu Asn Thr Ser Arg Arg Leu Leu His Pro Lys Asp Gln
705
710
715
720

```



## SEQUENCE LISTING 1657-2022.txt

Glu Val Phe Leu Lys Thr Lys Asp Asp Ala Ile Asn Gly Asp Lys Lys  
 725 730 735  
 Ala Lys Lys Gly Arg Arg Lys Leu Lys Leu Trp Lys His Ser Glu Lys  
 740 745 750  
 Glu Pro Glu Thr Asn Val Ala Glu Gly Arg Arg Val Phe Glu Ser Arg  
 755 760 765  
 Arg Arg Ile Asn Met Ala Asn Lys Gln Ile Asn Pro Glu Arg Trp Ala  
 770 775 780  
 Asp Ile Leu Ala Lys Val Arg Gly Lys Asn Leu Pro Lys Gly Thr Glu  
 785 790 795 800  
 Val Pro Pro Leu Ile Lys Thr Thr Ser Pro Pro Ser Leu Ser Leu Glu  
 805 810 815  
 Val Thr Pro Pro Phe Pro Ala Val Ser Pro Pro Ser Ala Ser Pro Val  
 820 825 830  
 Gln Thr Val Thr Ser Ala Glu Glu Ser Ser Ala Asp Val Pro Leu Leu  
 835 840 845  
 Gly Glu Glu Glu His Val Leu Gly Thr Ile Ser Ser Ala Ser Met Gly  
 850 855 860  
 Leu Glu His Asn His Asn Gly Val Ile Leu Val Glu Pro Glu Val Thr  
 865 870 875 880  
 Ser Thr Pro Leu Glu Val Val Asp Asp Leu Ser Glu Lys Thr Glu  
 885 890 895  
 Glu Ile Thr Ser Thr Glu Gly Asp Leu Lys Gly Thr Ala Ala Pro Thr  
 900 905 910  
 Leu Ile Ser Glu Pro Tyr Glu Pro Ser Pro Thr Leu His Thr Leu Asp  
 915 920 925  
 Thr Val Tyr Glu Lys Pro Thr His Glu Glu Thr Ala Thr Glu Gly Trp  
 930 935 940  
 Ser Ala Ala Asp Val Gly Ser Ser Pro Glu Pro Thr Ser Ser Glu Tyr  
 945 950 955 960  
 Glu Pro Pro Leu Asp Ala Val Ser Leu Ala Glu Ser Glu Pro Met Gln  
 965 970 975  
 Tyr Phe Asp Pro Asp Leu Glu Thr Lys Ser Gln Pro Asp Glu Asp Lys  
 980 985 990  
 Met Lys Glu Asp Thr Phe Ala His Leu Thr Pro Thr Pro Thr Ile Trp  
 995 1000 1005  
 Val Asn Asp Ser Ser Thr Ser Gln Leu Phe Glu Asp Ser Thr Ile Gly  
 1010 1015 1020  
 Glu Pro Gly Val Pro Gly Gln Ser His Leu Gln Gly Leu Thr Asp Asn  
 1025 1030 1035 1040  
 Ile His Leu Val Lys Ser Ser Leu Ser Thr Gln Asp Thr Leu Leu Ile  
 1045 1050 1055  
 Lys Lys Gly Met Lys Glu Met Ser Gln Thr Leu Gln Gly Gly Asn Met  
 1060 1065 1070  
 Leu Glu Gly Asp Pro Thr His Ser Arg Ser Ser Glu Ser Glu Gly Gln  
 1075 1080 1085  
 Glu Ser Lys Ser Ile Thr Leu Pro Asp Ser Thr Leu Gly Ile Met Ser  
 1090 1095 1100  
 Ser Met Ser Pro Val Lys Lys Pro Ala Glu Thr Thr Val Gly Thr Leu  
 1105 1110 1115 1120  
 Leu Asp Lys Asp Thr Thr Thr Val Thr Thr Thr Pro Arg Gln Lys Val  
 1125 1130 1135  
 Ala Pro Ser Ser Thr Met Ser Thr His Pro Ser Arg Arg Pro Asn  
 1140 1145 1150  
 Gly Arg Arg Arg Leu Arg Pro Asn Lys Phe Arg His Arg His Lys Gln  
 1155 1160 1165  
 Thr Pro Pro Thr Thr Phe Ala Pro Ser Glu Thr Phe Ser Thr Gln Pro  
 1170 1175 1180  
 Thr Gln Ala Pro Asp Ile Lys Ile Ser Ser Gln Val Glu Ser Ser Leu  
 1185 1190 1195 1200  
 Val Pro Thr Ala Trp Val Asp Asn Thr Val Asn Thr Pro Lys Gln Leu  
 1205 1210 1215  
 Glu Met Glu Lys Asn Ala Glu Pro Thr Ser Lys Gly Thr Pro Arg Arg  
 1220 1225 1230  
 Lys His Gly Lys Arg Pro Asn Lys His Arg Tyr Thr Pro Ser Thr Val  
 1235 1240 1245  
 Ser Ser Arg Ala Ser Gly Ser Lys Pro Ser Pro Ser Pro Glu Asn Lys

## SEQUENCE LISTING 1657-2022.txt

1250 1255 1260  
His Arg Asn Ile Val Thr Pro Ser Ser Glu Thr Ile Leu Leu Pro Arg  
1265 1270 1275 1280  
Thr Val Ser Leu Lys Thr Glu Gly Pro Tyr Asp Ser Leu Asp Tyr Met  
1285 1290 1295  
Thr Thr Thr Arg Lys Ile Tyr Ser Ser Tyr Pro Lys Val Gln Glu Thr  
1300 1305 1310  
Leu Pro Val Thr Tyr Lys Pro Thr Ser Asp Gly Lys Glu Ile Lys Asp  
1315 1320 1325  
Asp Val Ala Thr Asn Val Asp Lys His Lys Ser Asp Ile Leu Val Thr  
1330 1335 1340  
Gly Glu Ser Ile Thr Asn Ala Ile Pro Thr Ser Arg Ser Leu Val Ser  
1345 1350 1355 1360  
Thr Met Gly Glu Phe Lys Glu Glu Ser Ser Pro Val Gly Phe Pro Gly  
1365 1370 1375  
Thr Pro Thr Trp Asn Pro Ser Arg Thr Ala Gln Pro Gly Arg Leu Gln  
1380 1385 1390  
Thr Asp Ile Pro Val Thr Thr Ser Gly Glu Asn Leu Thr Asp Pro Pro  
1395 1400 1405  
Leu Leu Lys Glu Leu Glu Asp Val Asp Phe Thr Ser Glu Phe Leu Ser  
1410 1415 1420  
Ser Leu Thr Val Ser Thr Pro Phe His Gln Glu Glu Ala Gly Ser Ser  
1425 1430 1435 1440  
Thr Thr Leu Ser Ser Ile Lys Val Glu Val Ala Ser Ser Gln Ala Glu  
1445 1450 1455  
Thr Thr Thr Leu Asp Gln Asp His Leu Glu Thr Thr Val Ala Ile Leu  
1460 1465 1470  
Leu Ser Glu Thr Arg Pro Gln Asn His Thr Pro Thr Ala Ala Arg Met  
1475 1480 1485  
Lys Glu Pro Ala Ser Ser Ser Pro Ser Thr Ile Leu Met Ser Leu Gly  
1490 1495 1500  
Gln Thr Thr Thr Thr Lys Pro Ala Leu Pro Ser Pro Arg Ile Ser Gln  
1505 1510 1515 1520  
Ala Ser Arg Asp Ser Lys Glu Asn Val Phe Leu Asn Tyr Val Gly Asn  
1525 1530 1535  
Pro Glu Thr Glu Ala Thr Pro Val Asn Asn Glu Gly Thr Gln His Met  
1540 1545 1550  
Ser Gly Pro Asn Glu Leu Ser Thr Pro Ser Ser Asp Arg Asp Ala Phe  
1555 1560 1565  
Asn Leu Ser Thr Lys Leu Glu Leu Lys Gln Val Phe Gly Ser Arg  
1570 1575 1580  
Ser Leu Pro Arg Gly Pro Asp Ser Gln Arg Gln Asp Gly Arg Val His  
1585 1590 1595 1600  
Ala Ser His Gln Leu Thr Arg Val Pro Ala Lys Pro Ile Leu Pro Thr  
1605 1610 1615  
Ala Thr Val Arg Leu Pro Glu Met Ser Thr Gln Ser Ala Ser Arg Tyr  
1620 1625 1630  
Phe Val Thr Ser Gln Ser Pro Arg His Trp Thr Asn Lys Pro Glu Ile  
1635 1640 1645  
Thr Thr Tyr Pro Ser Gly Ala Leu Pro Glu Asn Lys Gln Phe Thr Thr  
1650 1655 1660  
Pro Arg Leu Ser Ser Thr Thr Ile Pro Leu Pro Leu His Met Ser Lys  
1665 1670 1675 1680  
Pro Ser Ile Pro Ser Lys Phe Thr Asp Arg Arg Thr Asp Gln Phe Asn  
1685 1690 1695  
Gly Tyr Ser Lys Val Phe Gly Asn Asn Ile Pro Glu Ala Arg Asn  
1700 1705 1710  
Pro Val Gly Lys Pro Pro Ser Pro Arg Ile Pro His Tyr Ser Asn Gly  
1715 1720 1725  
Arg Leu Pro Phe Phe Thr Asn Lys Thr Leu Ser Phe Pro Gln Leu Gly  
1730 1735 1740  
Val Thr Arg Arg Pro Gln Ile Pro Thr Ser Pro Ala Pro Val Met Arg  
1745 1750 1755 1760  
Glu Arg Lys Val Ile Pro Gly Ser Tyr Asn Arg Ile His Ser His Ser  
1765 1770 1775  
Thr Phe His Leu Asp Phe Gly Pro Pro Ala Pro Pro Leu Leu His Thr  
1780 1785 1790

## SEQUENCE LISTING 1657-2022.txt

Pro Gln Thr Thr Gly Ser Pro Ser Thr Asn Leu Gln Asn Ile Pro Met  
 1795 1800 1805  
 Val Ser Ser Thr Gln Ser Ser Ile Ser Phe Ile Thr Ser Ser Val Gln  
 1810 1815 1820  
 Ser Ser Gly Ser Phe His Gln Ser Ser Ser Lys Phe Phe Ala Gly Gly  
 1825 1830 1835 1840  
 Pro Pro Ala Ser Lys Phe Trp Ser Leu Gly Glu Lys Pro Gln Ile Leu  
 1845 1850 1855  
 Thr Lys Ser Pro Gln Thr Val Ser Val Thr Ala Glu Thr Asp Thr Val  
 1860 1865 1870  
 Phe Pro Cys Glu Ala Thr Gly Lys Pro Lys Pro Phe Val Thr Trp Thr  
 1875 1880 1885  
 Lys Val Ser Thr Gly Ala Leu Met Thr Pro Asn Thr Arg Ile Gln Arg  
 1890 1895 1900  
 Phe Glu Val Leu Lys Asn Gly Thr Leu Val Ile Arg Lys Val Gln Val  
 1905 1910 1915 1920  
 Gln Asp Arg Gly Gln Tyr Met Cys Thr Ala Ser Asn Leu His Gly Leu  
 1925 1930 1935  
 Asp Arg Met Val Val Leu Leu Ser Val Thr Val Gln Gln Pro Gln Ile  
 1940 1945 1950  
 Leu Ala Ser His Tyr Gln Asp Val Thr Val Tyr Leu Gly Asp Thr Ile  
 1955 1960 1965  
 Ala Met Glu Cys Leu Ala Lys Gly Thr Pro Ala Pro Gln Ile Ser Trp  
 1970 1975 1980  
 Ile Phe Pro Asp Arg Arg Val Trp Gln Thr Val Ser Pro Val Glu Ser  
 1985 1990 1995 2000  
 Arg Ile Thr Leu His Glu Asn Arg Thr Leu Ser Ile Lys Glu Ala Ser  
 2005 2010 2015  
 Phe Ser Asp Arg Gly Val Tyr Lys Cys Val Ala Ser Asn Ala Ala Gly  
 2020 2025 2030  
 Ala Asp Ser Leu Ala Ile Arg Leu His Val Ala Ala Leu Pro Pro Val  
 2035 2040 2045  
 Ile His Gln Glu Lys Leu Glu Asn Ile Ser Leu Pro Pro Gly Leu Ser  
 2050 2055 2060  
 Ile His Ile His Cys Thr Ala Lys Ala Ala Pro Leu Pro Ser Val Arg  
 2065 2070 2075 2080  
 Trp Val Leu Gly Asp Gly Thr Gln Ile Arg Pro Ser Gln Phe Leu His  
 2085 2090 2095  
 Gly Asn Leu Phe Val Phe Pro Asn Gly Thr Leu Tyr Ile Arg Asn Leu  
 2100 2105 2110  
 Ala Pro Lys Asp Ser Gly Arg Tyr Glu Cys Val Ala Ala Asn Leu Val  
 2115 2120 2125  
 Gly Ser Ala Arg Arg Thr Val Gln Leu Asn Val Gln Arg Ala Ala Ala  
 2130 2135 2140  
 Asn Ala Arg Ile Thr Gly Thr Ser Pro Arg Arg Thr Asp Val Arg Tyr  
 2145 2150 2155 2160  
 Gly Gly Thr Leu Lys Leu Asp Cys Ser Ala Ser Gly Asp Pro Trp Pro  
 2165 2170 2175  
 Arg Ile Leu Trp Arg Leu Pro Ser Lys Arg Met Ile Asp Ala Leu Phe  
 2180 2185 2190  
 Ser Phe Asp Ser Arg Ile Lys Val Phe Ala Asn Gly Thr Leu Val Val  
 2195 2200 2205  
 Lys Ser Val Thr Asp Lys Asp Ala Gly Asp Tyr Leu Cys Val Ala Arg  
 2210 2215 2220  
 Asn Lys Val Gly Asp Asp Tyr Val Val Leu Lys Val Asp Val Val Met  
 2225 2230 2235 2240  
 Lys Pro Ala Lys Ile Glu His Lys Glu Glu Asn Asp His Lys Val Phe  
 2245 2250 2255  
 Tyr Gly Gly Asp Leu Lys Val Asp Cys Val Ala Thr Gly Leu Pro Asn  
 2260 2265 2270  
 Pro Glu Ile Ser Trp Ser Leu Pro Asp Gly Ser Leu Val Asn Ser Phe  
 2275 2280 2285  
 Met Gln Ser Asp Asp Ser Gly Gly Arg Thr Lys Arg Tyr Val Val Phe  
 2290 2295 2300  
 Asn Asn Gly Thr Leu Tyr Phe Asn Glu Val Gly Met Arg Glu Glu Gly  
 2305 2310 2315 2320  
 Asp Tyr Thr Cys Phe Ala Glu Asn Gln Val Gly Lys Asp Glu Met Arg

## SEQUENCE LISTING 1657-2022.txt

Val Arg Val Lys Val Val Thr Ala Pro Ala Thr Ile Arg Asn Lys Thr  
 Tyr Leu Ala Val Gln Val Pro Tyr Gly Asp Val Val Thr Val Ala Cys  
 Glu Ala Lys Gly Glu Pro Met Pro Lys Val Thr Trp Leu Ser Pro Thr  
 Asn Lys Val Ile Pro Thr Ser Ser Glu Lys Tyr Gln Ile Tyr Gln Asp  
 Gly Thr Leu Leu Ile Gln Lys Ala Gln Arg Ser Asp Ser Gly Asn Tyr  
 Thr Cys Leu Val Arg Asn Ser Ala Gly Glu Asp Arg Lys Thr Val Trp  
 Ile His Val Asn Val Gln Pro Pro Lys Ile Asn Gly Asn Pro Asn Pro  
 Ile Thr Thr Val Arg Glu Ile Ala Ala Gly Gly Ser Arg Lys Leu Ile  
 Asp Cys Lys Ala Glu Gly Ile Pro Thr Pro Arg Val Leu Trp Ala Phe  
 Pro Glu Gly Val Val Leu Pro Ala Pro Tyr Tyr Gly Asn Arg Ile Thr  
 Val His Gly Asn Gly Ser Leu Asp Ile Arg Ser Leu Arg Lys Ser Asp  
 Ser Val Gln Leu Val Cys Met Ala Arg Asn Glu Gly Gly Glu Ala Arg  
 Leu Ile Val Gln Leu Thr Val Leu Glu Pro Met Glu Lys Pro Ile Phe  
 His Asp Pro Ile Ser Glu Lys Ile Thr Ala Met Ala Gly His Thr Ile  
 Ser Leu Asn Cys Ser Ala Ala Gly Thr Pro Thr Pro Ser Leu Val Trp  
 Val Leu Pro Asn Gly Thr Asp Leu Gln Ser Gly Gln Gln Leu Gln Arg  
 Phe Tyr His Lys Ala Asp Gly Met Leu His Ile Ser Gly Leu Ser Ser  
 Val Asp Ala Gly Ala Tyr Arg Cys Val Ala Arg Asn Ala Ala Gly His  
 Thr Glu Arg Leu Val Ser Leu Lys Val Gly Leu Lys Pro Glu Ala Asn  
 Lys Gln Tyr His Asn Leu Val Ser Ile Ile Asn Gly Glu Thr Leu Lys  
 Leu Pro Cys Thr Pro Pro Gly Ala Gly Gln Gly Arg Phe Ser Trp Thr  
 Leu Pro Asn Gly Met His Leu Glu Gly Pro Gln Thr Leu Gly Arg Val  
 Ser Leu Leu Asp Asn Gly Thr Leu Thr Val Arg Glu Ala Ser Val Phe  
 Asp Arg Gly Thr Tyr Val Cys Arg Met Glu Thr Glu Tyr Gly Pro Ser  
 Val Thr Ser Ile Pro Val Ile Val Ile Ala Tyr Pro Pro Arg Ile Thr  
 Ser Glu Pro Thr Pro Val Ile Tyr Thr Arg Pro Gly Asn Thr Val Lys  
 Leu Asn Cys Met Ala Met Gly Ile Pro Lys Ala Asp Ile Thr Trp Glu  
 Leu Pro Asp Lys Ser His Leu Lys Ala Gly Val Gln Ala Arg Leu Tyr  
 Gly Asn Arg Phe Leu His Pro Gln Gly Ser Leu Thr Ile Gln His Ala  
 Thr Gln Arg Asp Ala Gly Phe Tyr Lys Cys Met Ala Lys Asn Ile Leu  
 Gly Ser Asp Ser Lys Thr Thr Tyr Ile His Val Phe

<210> 125  
 <211> 1464

## SEQUENCE LISTING 1657-2022.txt

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 125

```

Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Ala Ala Thr
1      5      10      15
Ala Leu Leu Thr His Gly Gln Glu Gly Gln Val Glu Gly Gln Asp
20      25      30
Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His
35      40      45
Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp
50      55      60
Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn
65      70      75      80
Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro
85      90      95
Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly
100      105      110
Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro
115      120      125
Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Gly Gly Asn Phe Ala
130      135      140      145
Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala
145      150      155      160
Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Thr Gly Gly Ile Ser
165      170      175
Val Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Pro Gly Pro
180      185      190
Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro
195      200      205
Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly
210      215      220
Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg
225      230      235      240
Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro
245      250      255
Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly
260      265      270
Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu
275      280      285
Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg
290      295      300
Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly
305      310      315      320
Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro
325      330      335
Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys
340      345      350
Gly Glu Ala Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly
355      360      365
Val Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala Gly Pro
370      375      380
Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn
385      390      395      400
Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly
405      410      415
Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn
420      425      430
Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys
435      440      445
Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly
450      455      460
Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu
465      470      475      480
Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro
485      490      495
Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly

```

## SEQUENCE LISTING 1657-2022.txt

500  
 Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg  
 515  
 Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro  
 530  
 Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly  
 545  
 Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln  
 560  
 Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro  
 575  
 Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly  
 590  
 Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro  
 605  
 Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro  
 620  
 Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly  
 635  
 Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro  
 650  
 Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln  
 665  
 Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly  
 680  
 Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser  
 695  
 Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala  
 710  
 Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly  
 725  
 Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro  
 740  
 Ile Gly Pro Pro Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly  
 755  
 Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly  
 770  
 Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro  
 785  
 Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala  
 800  
 Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly  
 815  
 Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala  
 830  
 Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala  
 845  
 Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly  
 860  
 Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu  
 875  
 Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro  
 890  
 Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly  
 905  
 Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val  
 920  
 Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro  
 935  
 Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly  
 950  
 Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro  
 965  
 Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Ala Ala Glu Gly Ser Pro  
 980  
 Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly  
 995  
 1000  
 1010  
 1015  
 1020  
 1025  
 1030  
 1035  
 1040

## SEQUENCE LISTING 1657-2022.txt

Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Pro  
 1045 1050 1055  
 Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala  
 1060 1065 1070  
 Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly  
 1075 1080 1085  
 Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp  
 1090 1095 1100  
 Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro  
 1105 1110 1115 1120  
 Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly  
 1125 1130 1135  
 Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly Lys  
 1140 1145 1150  
 Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg  
 1155 1160 1165  
 Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro Gly  
 1170 1175 1180  
 Pro Pro Gly Pro Pro Gly Pro Pro Ser Ala Gly Phe Asp Phe Ser Phe  
 1185 1190 1195 1200  
 Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr  
 1205 1210 1215  
 Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp  
 1220 1225 1230  
 Thr Thr Leu Lys Ser Leu Ser Gln Ile Glu Asn Ile Arg Ser Pro  
 1235 1240 1245  
 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met  
 1250 1255 1260  
 Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln  
 1265 1270 1275 1280  
 Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly  
 1285 1290 1295  
 Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp  
 1300 1305 1310  
 Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu  
 1315 1320 1325  
 Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp  
 1330 1335 1340  
 Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr  
 1345 1350 1355 1360  
 Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr  
 1365 1370 1375  
 Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Lys Gly  
 1380 1385 1390  
 Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr  
 1395 1400 1405  
 Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys  
 1410 1415 1420  
 Thr Val Ile Glu Tyr Lys Thr Thr Lys Ser Ser Arg Leu Pro Ile Ile  
 1425 1430 1435 1440  
 Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe  
 1445 1450 1455  
 Asp Val Gly Pro Val Cys Phe Leu  
 1460

<210> 126  
 <211> 308  
 <212> PRT  
 <213> Homo sapiens

<400> 126  
 Met Pro Gly Gln Glu Leu Arg Thr Val Asn Gly Ser Gln Met Leu Leu  
 1 5 10 15  
 Val Leu Leu Val Leu Ser Trp Leu Pro His Gly Gly Ala Leu Ser Leu  
 20 25 30  
 Ala Glu Ala Ser Arg Ala Ser Phe Pro Gly Pro Ser Glu Leu His Ser

## SEQUENCE LISTING 1657-2022.txt

```

      35      40      45
Glu Asp Ser Arg Phe Arg Glu Leu Arg Lys Arg Tyr Glu Asp Leu Leu
 50      55      60
Thr Arg Leu Arg Ala Asn Gln Ser Trp Glu Asp Ser Asn Thr Asp Leu
 65      70      75      80
Val Pro Ala Pro Ala Val Arg Ile Leu Thr Pro Glu Val Arg Leu Gly
      85      90      95
Ser Gly Gly His Leu His Leu Arg Ile Ser Arg Ala Ala Leu Pro Glu
 100      105      110
Gly Leu Pro Glu Ala Ser Arg Leu His Arg Ala Leu Phe Arg Leu Ser
 115      120      125
Pro Thr Ala Ser Arg Ser Trp Asp Val Thr Arg Pro Leu Arg Arg Gln
 130      135      140
Leu Ser Leu Ala Arg Pro Gln Ala Pro Ala Leu His Leu Arg Leu Ser
 145      150      155      160
Pro Pro Pro Ser Gln Ser Asp Gln Leu Leu Ala Glu Ser Ser Ser Ala
      165      170      175
Arg Pro Gln Leu Glu Leu His Leu Arg Pro Gln Ala Ala Arg Gly Arg
 180      185      190
Arg Arg Ala Arg Ala Arg Asn Gly Asp Asp Cys Pro Leu Gly Pro Gly
 195      200      205
Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly
 210      215      220
Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys
 225      230      235      240
Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln
      245      250      255
Ile Lys Thr Ser Leu His Arg Leu Lys Pro Asp Thr Glu Pro Ala Pro
 260      265      270
Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr
 275      280      285
Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp
 290      295      300
Cys His Cys Ile
305

```

<210> 127  
 <211> 359  
 <212> PRT  
 <213> Homo sapiens

```

<400> 127
Met Pro Ala His Leu Leu Gln Asp Asp Ile Ser Ser Ser Tyr Thr Thr
 1      5      10      15
Thr Thr Thr Ile Thr Ala Pro Pro Ser Arg Val Leu Gln Asn Gly Gly
 20      25      30
Asp Lys Leu Glu Thr Met Pro Leu Tyr Leu Glu Asp Asp Ile Arg Pro
 35      40      45
Asp Ile Lys Asp Asp Ile Tyr Asp Pro Thr Tyr Lys Asp Lys Glu Gly
 50      55      60
Pro Ser Pro Lys Val Glu Tyr Val Trp Arg Asn Ile Ile Leu Met Ser
 65      70      75      80
Leu Leu His Leu Gly Ala Leu Tyr Gly Ile Thr Leu Ile Pro Thr Cys
      85      90      95
Lys Phe Tyr Thr Trp Leu Trp Gly Val Phe Tyr Tyr Phe Val Ser Ala
 100      105      110
Leu Gly Ile Thr Ala Gly Ala His Arg Leu Trp Ser His Arg Ser Tyr
 115      120      125
Lys Ala Arg Leu Pro Leu Arg Leu Phe Leu Ile Ile Ala Asn Thr Met
 130      135      140
Ala Phe Gln Asn Asp Val Tyr Glu Trp Ala Arg Asp His Arg Ala His
 145      150      155      160
His Lys Phe Ser Glu Thr His Ala Asp Pro His Asn Ser Arg Arg Gly
      165      170      175
Phe Phe Phe Ser His Val Gly Trp Leu Leu Val Arg Lys His Pro Ala
 180      185      190

```



## SEQUENCE LISTING 1657-2022.txt

Val Lys Glu Lys Gly Ser Thr Leu Asp Leu Ser Asp Leu Glu Ala Glu  
 195 200 205  
 Lys Leu Val Met Phe Gln Arg Arg Tyr Tyr Lys Pro Gly Leu Leu Leu  
 210 215 220  
 Met Cys Phe Ile Leu Pro Thr Leu Val Pro Trp Tyr Phe Trp Gly Glu  
 225 230 235 240  
 Thr Phe Gln Asn Ser Val Phe Val Ala Thr Phe Leu Arg Tyr Ala Val  
 245 250 255  
 Val Leu Asn Ala Thr Trp Leu Val Asn Ser Ala Ala His Leu Phe Gly  
 260 265 270  
 Tyr Arg Pro Tyr Asp Lys Asn Ile Ser Pro Arg Glu Asn Ile Leu Val  
 275 280 285  
 Ser Leu Gly Ala Val Gly Glu Gly Phe His Asn Tyr His His Ser Phe  
 290 295 300  
 Pro Tyr Asp Tyr Ser Ala Ser Glu Tyr Arg Trp His Ile Asn Phe Thr  
 305 310 315 320  
 Thr Phe Phe Ile Asp Cys Met Ala Ala Leu Gly Leu Ala Tyr Asp Arg  
 325 330 335  
 Lys Lys Val Ser Lys Ala Ala Ile Leu Ala Arg Ile Lys Arg Thr Gly  
 340 345 350  
 Asp Gly Asn Tyr Lys Ser Gly  
 355

<210> 128  
 <211> 96  
 <212> PRT  
 <213> Homo sapiens

<400> 128  
 Met Cys Cys Thr Lys Ser Leu Leu Leu Ala Ala Leu Met Ser Val Leu  
 1 5 10 15  
 Leu Leu His Leu Cys Gly Glu Ser Glu Ala Ala Ser Asn Phe Asp Cys  
 20 25 30  
 Cys Leu Gly Tyr Thr Asp Arg Ile Leu His Pro Lys Phe Ile Val Gly  
 35 40 45  
 Phe Thr Arg Gln Leu Ala Asn Glu Gly Cys Asp Ile Asn Ala Ile Ile  
 50 55 60  
 Phe His Thr Lys Lys Lys Leu Ser Val Cys Ala Asn Pro Lys Gln Thr  
 65 70 75 80  
 Trp Val Lys Tyr Ile Val Arg Leu Leu Ser Lys Lys Val Lys Asn Met  
 85 90 95

<210> 129  
 <211> 518  
 <212> PRT  
 <213> Homo sapiens

<400> 129  
 Met Gly Ala Leu Ala Arg Ala Leu Leu Leu Pro Leu Leu Ala Gln Trp  
 1 5 10 15  
 Leu Leu Arg Ala Ala Pro Glu Leu Ala Pro Ala Pro Phe Thr Leu Pro  
 20 25 30  
 Leu Arg Val Ala Ala Ala Thr Asn Arg Val Val Ala Pro Thr Pro Gly  
 35 40 45  
 Pro Gly Thr Pro Ala Glu Arg His Ala Asp Gly Leu Ala Leu  
 50 55 60  
 Glu Pro Ala Leu Ala Ser Pro Ala Gly Ala Ala Asn Phe Leu Ala Met  
 65 70 75 80  
 Val Asp Asn Leu Gln Gly Asp Ser Gly Arg Gly Tyr Tyr Leu Glu Met  
 85 90 95  
 Leu Ile Gly Thr Pro Pro Gln Lys Leu Gln Ile Leu Val Asp Thr Gly  
 100 105 110  
 Ser Ser Asn Phe Ala Val Ala Gly Thr Pro His Ser Tyr Ile Asp Thr  
 115 120 125  
 Tyr Phe Asp Thr Glu Arg Ser Ser Thr Tyr Arg Ser Lys Gly Phe Asp

## SEQUENCE LISTING 1657-2022.txt

```

130      135      140
Val Thr Val Lys Tyr Thr Gln Gly Ser Trp Thr Gly Phe Val Gly Glu
145      150      155
Asp Leu Val Thr Ile Pro Lys Gly Phe Asn Thr Ser Phe Leu Val Asn
165
Ile Ala Thr Ile Phe Glu Ser Glu Asn Phe Phe Leu Pro Gly Ile Lys
180      185
Trp Asn Gly Ile Leu Gly Leu Ala Tyr Ala Thr Leu Ala Lys Pro Ser
195      200
Ser Ser Leu Glu Thr Phe Phe Asp Ser Leu Val Thr Gln Ala Asn Ile
210      215      220
Pro Asn Val Phe Ser Met Gln Met Cys Gly Ala Gly Leu Pro Val Ala
225      230      235
Gly Ser Gly Thr Asn Gly Gly Ser Leu Val Leu Gly Gly Ile Glu Pro
245      250      255
Ser Leu Tyr Lys Gly Asp Ile Trp Tyr Thr Pro Ile Lys Glu Glu Trp
260      265      270
Tyr Tyr Gln Ile Glu Ile Leu Lys Leu Glu Ile Gly Gly Gln Ser Leu
275      280      285
Asn Leu Asp Cys Arg Glu Tyr Asn Ala Asp Lys Ala Ile Val Asp Ser
290      295      300
Gly Thr Thr Leu Leu Arg Leu Pro Gln Lys Val Phe Asp Ala Val Val
305      310      315
Glu Ala Val Ala Arg Ala Ser Leu Ile Pro Glu Phe Ser Asp Gly Phe
325      330      335
Trp Thr Gly Ser Gln Leu Ala Cys Trp Thr Asn Ser Glu Thr Pro Trp
340      345      350
Ser Tyr Phe Pro Lys Ile Ser Ile Tyr Leu Arg Asp Glu Asn Ser Ser
355      360      365
Arg Ser Phe Arg Ile Thr Ile Leu Pro Gln Leu Tyr Ile Gln Pro Met
370      375      380
Met Gly Ala Gly Leu Asn Tyr Glu Cys Tyr Arg Phe Gly Ile Ser Pro
385      390      395
Ser Thr Asn Ala Leu Val Ile Gly Ala Thr Val Met Glu Gly Phe Tyr
405      410      415
Val Ile Phe Asp Arg Ala Gln Lys Arg Val Gly Phe Ala Ala Ser Pro
420      425      430
Cys Ala Glu Ile Ala Gly Ala Ala Val Ser Glu Ile Ser Gly Pro Phe
435      440      445
Ser Thr Glu Asp Val Ala Ser Asn Cys Val Pro Ala Gln Ser Leu Ser
450      455      460
Glu Pro Ile Leu Trp Ile Val Ser Tyr Ala Leu Met Ser Val Cys Gly
465      470      475
Ala Ile Leu Leu Val Leu Ile Val Leu Leu Leu Pro Phe Arg Cys
485      490      495
Gln Arg Arg Pro Arg Asp Pro Glu Val Val Asn Asp Glu Ser Ser Leu
500      505      510
Val Arg His Arg Trp Lys
515

```

```

<210> 130
<211> 423
<212> PRT
<213> Homo sapiens

```

```

<400> 130
Met Arg Ser Ser Gly Ala Asp Ala Gly Arg Cys Leu Val Thr Ala Arg
1      5      10      15
Ala Pro Gly Ser Val Pro Ala Ser Arg Glu Gly Ser Ala Gly Ser Arg
20      25      30
Gly Pro Gly Ala Arg Phe Pro Ala Arg Val Ser Ala Arg Gly Ser Ala
35      40      45
Pro Gly Pro Gly Leu Gly Gly Ala Gly Ala Leu Asp Pro Pro Ala Val
50      55      60
Val Ala Glu Ser Val Ser Ser Leu Thr Ile Ala Asp Ala Phe Ile Ala
65      70      75      80

```

## SEQUENCE LISTING 1657-2022.txt

Ala Gly Glu Ser Ser Ala Pro Thr Pro Arg Pro Ala Leu Pro Arg  
 85 90 95  
 Arg Phe Ile Cys Ser Phe Pro Asp Cys Ser Ala Asn Tyr Ser Lys Ala  
 100 105 110  
 Trp Lys Leu Asp Ala His Leu Cys Lys His Thr Gly Glu Arg Pro Phe  
 115 120 125  
 Val Cys Asp Tyr Glu Gly Cys Gly Lys Ala Phe Ile Arg Asp Tyr His  
 130 135 140  
 Leu Ser Arg His Ile Leu Thr His Thr Gly Glu Lys Pro Phe Val Cys  
 145 150 155 160  
 Ala Ala Asn Gly Cys Asp Gln Lys Phe Asn Thr Lys Ser Asn Leu Lys  
 165 170 175  
 Lys His Phe Glu Arg Lys His Glu Asn Gln Gln Lys Gln Tyr Ile Cys  
 180 185 190  
 Ser Phe Glu Asp Cys Lys Lys Thr Phe Lys Lys His Gln Gln Leu Lys  
 195 200 205  
 Ile His Gln Cys Gln Asn Thr Asn Glu Pro Leu Phe Lys Cys Thr Gln  
 210 215 220  
 Glu Gly Cys Gly Lys His Phe Ala Ser Pro Ser Lys Leu Lys Arg His  
 225 230 235 240  
 Ala Lys Ala His Glu Gly Tyr Val Cys Gln Lys Gly Cys Ser Phe Val  
 245 250 255  
 Ala Lys Thr Trp Thr Glu Leu Leu Lys His Val Arg Glu Thr His Lys  
 260 265 270  
 Glu Glu Ile Leu Cys Glu Val Cys Arg Lys Thr Phe Lys Arg Lys Asp  
 275 280 285  
 Tyr Leu Lys Gln His Met Lys Thr His Ala Pro Glu Arg Asp Val Cys  
 290 295 300  
 Arg Cys Pro Arg Glu Gly Cys Gly Arg Thr Tyr Thr Thr Val Phe Asn  
 305 310 315 320  
 Leu Gln Ser His Ile Leu Ser Phe His Glu Glu Ser Arg Pro Phe Val  
 325 330 335  
 Cys Glu His Ala Gly Cys Gly Lys Thr Phe Ala Met Lys Gln Ser Leu  
 340 345 350  
 Thr Arg His Ala Val Val His Asp Pro Asp Lys Lys Lys Met Lys Leu  
 355 360 365  
 Lys Val Lys Lys Ser Arg Glu Lys Arg Glu Phe Gly Leu Ser Ser Gln  
 370 375 380  
 Trp Ile Tyr Pro Pro Lys Arg Lys Gln Gly Gln Gly Leu Ser Leu Cys  
 385 390 395 400  
 Gln Asn Gly Glu Ser Pro Asn Cys Val Glu Asp Lys Met Leu Ser Thr  
 405 410 415  
 Val Ala Val Leu Thr Leu Gly  
 420

<210> 131  
 <211> 677  
 <212> PRT  
 <213> Homo sapiens

<400> 131  
 Met Leu Ser Ser Thr Asp Phe Thr Phe Ala Ser Trp Glu Leu Val Val  
 1 5 10 15  
 Arg Val Asp His Pro Asn Glu Glu Gln Gln Lys Asp Val Thr Leu Arg  
 20 25 30  
 Val Ser Gly Asp Leu His Val Gly Gly Val Met Leu Lys Leu Val Glu  
 35 40 45  
 Gln Ile Asn Ile Ser Gln Asp Trp Ser Asp Phe Ala Leu Trp Trp Glu  
 50 55 60  
 Gln Lys His Cys Trp Leu Lys Thr His Trp Thr Leu Asp Lys Tyr  
 65 70 75 80  
 Gly Val Gln Ala Asp Ala Lys Leu Leu Phe Thr Pro Gln His Lys Met  
 85 90 95  
 Leu Arg Leu Arg Leu Pro Asn Leu Lys Met Val Arg Leu Arg Val Ser  
 100 105 110  
 Phe Ser Ala Val Val Phe Lys Ala Val Ser Asp Ile Cys Lys Ile Leu

## SEQUENCE LISTING 1657-2022.txt

```

115      120      125
Asn Ile Arg Arg Ser Glu Glu Leu Ser Leu Leu Lys Pro Ser Gly Asp
130      135      140
Tyr Phe Lys Lys Lys Lys Lys Asp Lys Asn Asn Lys Glu Pro Ile
145      150      155
Ile Glu Asp Ile Leu Asn Leu Glu Ser Ser Pro Thr Ala Ser Gly Ser
165      170      175
Ser Val Ser Pro Gly Leu Tyr Ser Lys Thr Met Thr Pro Ile Tyr Asp
180      185      190
Pro Ile Asn Gly Thr Pro Ala Ser Ser Thr Met Thr Trp Phe Ser Asp
195      200      205
Ser Pro Leu Thr Glu Gln Asn Cys Ser Ile Leu Ala Phe Ser Gln Pro
210      215      220
Pro Gln Ser Pro Glu Ala Leu Ala Asp Met Tyr Gln Pro Arg Ser Leu
225      230      235
Val Asp Lys Ala Lys Leu Asn Ala Gly Trp Leu Asp Ser Ser Arg Ser
245      250      255
Leu Met Glu Gln Gly Ile Gln Glu Asp Glu Gln Leu Leu Leu Arg Phe
260      265      270
Lys Tyr Tyr Ser Phe Phe Asp Leu Asn Pro Lys Tyr Asp Ala Val Arg
275      280      285
Ile Asn Gln Leu Tyr Glu Gln Ala Arg Trp Ala Ile Leu Leu Glu Glu
290      295      300
Ile Asp Cys Thr Glu Glu Glu Met Leu Ile Phe Ala Ala Leu Gln Tyr
305      310      315
His Ile Ser Lys Leu Ser Leu Ser Ala Glu Thr Gln Asp Phe Ala Gly
325      330      335
Glu Ser Glu Val Asp Glu Ile Glu Ala Leu Ser Asn Leu Glu Val
340      345      350
Thr Leu Glu Gly Gly Lys Ala Asp Ser Leu Leu Glu Asp Ile Thr Asp
355      360      365
Ile Pro Lys Leu Ala Asp Asn Leu Lys Leu Phe Arg Pro Lys Lys Leu
370      375      380
Leu Pro Lys Ala Phe Lys Gln Tyr Trp Phe Ile Phe Lys Asp Thr Ser
385      390      395
Ile Ala Tyr Phe Lys Asn Lys Glu Leu Glu Gln Gly Glu Pro Leu Glu
400      405      410
Lys Leu Asn Leu Arg Gly Cys Glu Val Val Pro Asp Val Asn Val Ala
415      420      425
Gly Arg Lys Phe Gly Ile Lys Leu Leu Ile Pro Val Ala Asp Gly Met
430      435      440
Asn Glu Met Tyr Leu Arg Cys Asp His Glu Asn Gln Tyr Ala Gln Trp
445      450      455
Met Ala Ala Cys Met Leu Ala Ser Lys Gly Lys Thr Met Ala Asp Ser
460      465      470
Ser Tyr Gln Pro Glu Val Leu Asn Ile Leu Ser Phe Leu Arg Met Lys
475      480      485
Asn Arg Asn Ser Ala Ser Gln Val Ala Ser Ser Leu Glu Asn Met Asp
490      495      500
Met Asn Pro Glu Cys Phe Val Ser Pro Arg Cys Ala Lys Lys His Lys
505      510      515
Ser Lys Gln Leu Ala Ala Arg Ile Leu Glu Ala His Gln Asn Val Ala
520      525      530
Gln Met Pro Leu Val Glu Ala Lys Leu Arg Phe Ile Gln Ala Trp Gln
535      540      545
Ser Leu Pro Glu Phe Gly Leu Thr Tyr Tyr Leu Val Arg Phe Lys Gly
550      555      560
Ser Lys Lys Asp Ile Leu Gly Val Ser Tyr Asn Arg Leu Ile Lys
565      570      575
Ile Asp Ala Ala Thr Gly Ile Pro Val Thr Thr Trp Arg Phe Thr Asn
580      585      590
Ile Lys Gln Trp Asn Val Asn Trp Glu Thr Arg Gln Val Val Ile Glu
595      600      605
Phe Asp Gln Asn Val Phe Thr Ala Phe Thr Cys Leu Ser Ala Asp Cys
610      615      620
Lys Ile Val His Glu Tyr Ile Gly Gly Tyr Ile Phe Leu Ser Thr Arg
625      630      635
645      650      655

```

## SEQUENCE LISTING 1657-2022.txt

Ser Lys Asp Gln Asn Glu Thr Leu Asp Glu Asp Leu Phe His Lys Leu  
 660 665 670  
 Thr Gly Gly Gln Asp  
 675

<210> 132  
 <211> 836  
 <212> PRT  
 <213> Homo sapiens

<400> 132  
 Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val  
 1 5 10 15  
 Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser  
 20 25 30  
 Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln  
 35 40 45  
 Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr  
 50 55 60  
 Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys  
 65 70 75 80  
 Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu  
 85 90 95  
 Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr  
 100 105 110  
 Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly  
 115 120 125  
 Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn  
 130 135 140  
 Leu Asp Ser Asp Ile Arg Arg Gly Leu Glu Ser Asn Val Asn Val Glu  
 145 150 155 160  
 Leu Leu Asn Ala Leu His Ser His Met Ile Asn Lys Arg Met Leu Thr  
 165 170 175  
 Lys Asp Leu Lys Asn Gly Met Ile Ile Pro Ser Met Tyr Asn Asn Leu  
 180 185 190  
 Gly Leu Phe Ile Asn His Tyr Pro Asn Gly Val Val Thr Val Asn Cys  
 195 200 205  
 Ala Arg Ile Ile His Gly Asn Gln Ile Ala Thr Asn Gly Val Val His  
 210 215 220  
 Val Ile Asp Arg Val Leu Thr Gln Ile Gly Thr Ser Ile Gln Asp Phe  
 225 230 235 240  
 Ile Glu Ala Glu Asp Asp Leu Ser Ser Phe Arg Ala Ala Ala Ile Thr  
 245 250 255  
 Ser Asp Ile Leu Glu Ala Leu Gly Arg Asp Gly His Phe Thr Leu Phe  
 260 265 270  
 Ala Pro Thr Asn Glu Ala Phe Glu Lys Leu Pro Arg Gly Val Leu Glu  
 275 280 285  
 Arg Phe Met Gly Asp Lys Val Ala Ser Glu Ala Leu Met Lys Tyr His  
 290 295 300  
 Ile Leu Asn Thr Leu Gln Cys Ser Glu Ser Ile Met Gly Gly Ala Val  
 305 310 315 320  
 Phe Glu Thr Leu Glu Gly Asn Thr Ile Glu Ile Gly Cys Asp Gly Asp  
 325 330 335  
 Ser Ile Thr Val Asn Gly Ile Lys Met Val Asn Lys Lys Asp Ile Val  
 340 345 350  
 Thr Asn Asn Gly Val Ile His Leu Ile Asp Gln Val Leu Ile Pro Asp  
 355 360 365  
 Ser Ala Lys Gln Val Ile Glu Leu Ala Gly Lys Gln Gln Thr Thr Phe  
 370 375 380  
 Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp  
 385 390 395 400  
 Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp  
 405 410 415  
 Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His  
 420 425 430  
 Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile  
 Page 115

## SEQUENCE LISTING 1657-2022.txt

435  
 Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr  
 450  
 Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly  
 465  
 Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu  
 485  
 Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe  
 500  
 Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro  
 515  
 Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met  
 530  
 Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln  
 545  
 Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly  
 565  
 Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys  
 580  
 Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys  
 595  
 Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val  
 610  
 Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu  
 625  
 Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val  
 645  
 Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys  
 660  
 Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser  
 675  
 Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys  
 690  
 Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile  
 705  
 Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile  
 725  
 Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu  
 740  
 Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly  
 755  
 Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val  
 770  
 Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu  
 785  
 Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys  
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 Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu  
 820  
 Gly Arg Ser Gln  
 835

<210> 133  
 <211> 303  
 <212> PRT  
 <213> Homo sapiens

<400> 133  
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 Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val  
 35 40 45  
 Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Thr Glu Glu  
 50 55 60

## SEQUENCE LISTING 1657-2022.txt

Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly  
 65 70 75 80  
 Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln  
 85 90 95  
 Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys  
 100 105 110  
 Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr  
 115 120 125  
 Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp  
 130 135 140  
 Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu  
 145 150 155 160  
 Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val  
 165 170 175  
 Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln  
 180 185 190  
 Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala  
 195 200 205  
 Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr  
 210 215 220  
 Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln  
 225 230 235 240  
 His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg  
 245 250 255  
 Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr  
 260 265 270  
 Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly  
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 Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile  
 290 295 300

<210> 134  
 <211> 683  
 <212> PRT  
 <213> Homo sapiens

<400> .134

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 Val Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val  
 35 40 45  
 Cys Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn  
 50 55 60  
 Cys Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile  
 65 70 75 80  
 Ser Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly  
 85 90 95  
 Cys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val  
 100 105 110  
 Val Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu  
 115 120 125  
 Arg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser  
 130 135 140  
 Asn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val  
 145 150 155 160  
 Ser Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val  
 165 170 175  
 Gly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr  
 180 185 190  
 Ser Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly  
 195 200 205  
 Ile Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala  
 210 215 220  
 Thr Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr

SEQUENCE LISTING 1657-2022.txt																		
225	Asn	Asn	Ile	Gln	Gln	Ile	Ile	Glu	Ile	Glu	235	Asp	Thr	Phe	Glu	Thr	240	Leu
Arg	Ala	Ala	Val	245	Ala	Ala	Ser	Gly	Leu	250	Asn	Thr	Met	Leu	Glu	255	Gly	Asn
Gly	Gln	Tyr	Thr	260	Leu	Leu	Ala	Pro	Thr	265	Asn	Glu	Ala	Phe	Glu	Lys	Ile	
Pro	Ser	Glu	Thr	275	Leu	Asn	Arg	Ile	Leu	280	Gly	Asp	Pro	285	Glu	Ala	Leu	Arg
Asp	Leu	Leu	Asn	Asn	His	Ile	Leu	Lys	Ser	300	Ala	Met	Cys	Ala	Glu	Ala	320	Glu
Ile	Val	Ala	Gly	Leu	310	Ser	Val	Glu	Thr	315	Glu	Gly	Thr	Thr	Leu	335	Ile	Ile
Val	Gly	Cys	Ser	Gly	325	Asp	Met	Leu	Thr	330	Ile	Asn	Gly	Lys	Ala	350	Ile	Ile
Ser	Asn	Lys	Asp	Ile	Leu	Ala	Thr	Asn	Gly	345	Val	Ile	His	365	Glu	Leu	Ala	Ala
Glu	Leu	Leu	Ile	Pro	Asp	Ser	Ala	Lys	Thr	370	Leu	Phe	380	Arg	Gln	Ala	Gly	Leu
Glu	Ser	Asp	Val	Ser	Thr	Ala	Ile	Asp	Leu	385	Phe	395	Thr	Leu	Leu	Ala	Pro	400
Gly	Asn	His	Leu	Ser	Gly	Ser	Glu	Arg	Leu	410	Thr	Leu	Leu	Ala	Pro	415	Thr	Arg
Asn	Ser	Val	Phe	Lys	Asp	Gly	Thr	Pro	425	Pro	Ile	Asp	Ala	His	430	Ser	Lys	Tyr
Asn	Leu	Leu	Arg	Asn	His	Ile	Ile	Lys	Asp	440	Gln	Leu	Ala	445	Lys	Lys	Leu	Arg
Leu	Tyr	His	Gly	Gln	Thr	Leu	Glu	Thr	Leu	450	Gly	Gly	460	Lys	Lys	Leu	Arg	
Val	Phe	Val	Tyr	Arg	Asn	Ser	Leu	Cys	Ile	465	Glu	Asn	Ser	Cys	Ile	Ala	480	Arg
Ala	His	Asp	Lys	Arg	Gly	Arg	Tyr	Gly	Thr	475	Leu	Phe	Thr	Met	Asp	495	Gly	Asp
Val	Leu	Thr	Pro	Pro	Met	Gly	Thr	Val	Met	500	Asp	Val	Leu	Lys	510	Gly	Leu	Thr
Asn	Arg	Phe	Ser	Met	Leu	Val	Ala	Ile	Gln	515	Ser	Ala	525	Ala	Pro	Thr	Asn	
Glu	Thr	Leu	Asn	Arg	Glu	Gly	Val	Tyr	Thr	530	Val	Phe	540	Ser	Arg	Leu	Leu	Gly
Glu	Ala	Phe	Arg	Ala	Leu	Pro	Pro	Arg	Glu	545	Arg	555	Tyr	His	Ile	Gly	Asp	560
Asp	Ala	Lys	Glu	Leu	Ala	Asn	Ile	Leu	Lys	570	Leu	Val	Arg	Leu	Lys	590	Ser	Leu
Ile	Leu	Val	Ser	Gly	Gly	Ile	Gly	Ala	Leu	585	Leu	Lys	Asn	Asn	Val	605	Thr	Asn
Gln	Gly	Asp	Lys	Leu	Glu	Val	Ser	Pro	Asp	600	Ile	Met	Ala	620	Thr	Asn	Gly	Val
Asn	Lys	Glu	Pro	Val	Ala	Glu	Val	Leu	Gln	615	Pro	Pro	Ala	Asn	Arg	Pro	Gln	640
Val	His	Val	Ile	Thr	Asn	Val	Leu	Gln	Pro	625	Pro	635	Leu	Glu	Ile	Phe	Lys	655
Glu	Arg	Gly	Asp	Glu	Leu	Ala	Asp	Ser	Ala	650	Arg	Ser	Val	Arg	Leu	Ala	Pro	
Ala	Ser	Ala	Phe	Ser	Arg	Ala	Ser	Gln	Arg	665	Ser	Val	Arg	Leu	670			
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<210> 135
<211> 2355
<212> PRT
<213> Homo sapiens
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<400> 135  
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## SEQUENCE LISTING 1657-2022.txt

Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln  
 20 25 30  
 Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser  
 35 40 45  
 Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln  
 50 55 60  
 Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly  
 65 70 75 80  
 Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr  
 85 90 95  
 Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr  
 100 105 110  
 Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala  
 115 120 125  
 Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly  
 130 135 140  
 Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr  
 145 150 155 160  
 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu  
 165 170 175  
 Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly  
 180 185 190  
 Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp  
 195 200 205  
 Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr  
 210 215 220  
 Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr  
 225 230 235 240  
 Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu  
 245 250 255  
 Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg  
 260 265 270  
 His Thr Ser Val Gln Thr Thr Ser Gly Ser Gly Pro Phe Thr Asp  
 275 280 285  
 Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro  
 290 295 300  
 Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met  
 305 310 315 320  
 Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu  
 325 330 335  
 Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly  
 340 345 350  
 Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly  
 355 360 365  
 Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu  
 370 375 380  
 Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe  
 385 390 395 400  
 Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn  
 405 410 415  
 Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr  
 420 425 430  
 Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly Thr  
 435 440 445  
 Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met Ala  
 450 455 460  
 Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg Ile  
 465 470 475 480  
 Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg Cys  
 485 490 495  
 Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr Ser  
 500 505 510  
 Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val Asn  
 515 520 525  
 Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys Thr  
 530 535 540  
 Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp Gln

## SEQUENCE LISTING 1657-2022.txt

545 Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser Trp  
 550 555 560  
 Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly Arg  
 565 570 575  
 Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser Ser  
 580 585 590  
 Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro Asn  
 595 600 605  
 Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser Lys  
 610 615 620  
 Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val Gly Arg Trp Lys Glu  
 625 630 635  
 Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr Ile Lys Gly Leu Lys  
 640 645 650  
 Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr Gly  
 655 660 665  
 His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser Thr  
 670 675 680  
 Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser Pro  
 685 690 695  
 Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser Phe  
 700 705 710  
 Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg Val  
 715 720 725  
 Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp Leu  
 730 735 740  
 Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly Arg  
 745 750 755  
 Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln Ser  
 760 765 770  
 Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro Asp  
 775 780 785  
 Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp Ser  
 790 795 800  
 Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro Ser  
 805 810 815  
 Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser  
 820 825 830  
 Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile  
 835 840 845  
 Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln  
 850 855 860  
 Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp  
 865 870 875  
 Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr  
 880 885 890  
 Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val  
 895 900 905  
 Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr  
 910 915 920  
 Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys  
 925 930 935  
 Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Thr Ala Gln  
 940 945 950  
 Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu  
 955 960 965  
 Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile  
 970 975 980  
 Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg  
 985 990 995  
 Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu  
 1000 1005 1010  
 Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn  
 1015 1020 1025  
 Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly  
 1030 1035 1040  
 1045 1050 1055  
 1060 1065 1070  
 1075 1080 1085

## SEQUENCE LISTING 1657-2022.txt

Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val  
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 Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg  
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 Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly  
 1125 1130 1135  
 Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr  
 1140 1145 1150  
 Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn  
 1155 1160 1165  
 Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala  
 1170 1175 1180  
 Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr  
 1185 1190 1195 1200  
 Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln  
 1205 1210 1215  
 Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys  
 1220 1225 1230  
 Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr  
 1235 1240 1245  
 Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile  
 1250 1255 1260  
 Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro  
 1265 1270 1275 1280  
 Asp Thr Met Arg Val Thr Trp Ala Pro Pro Ser Ile Asp Leu Thr  
 1285 1290 1295  
 Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala  
 1300 1305 1310  
 Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu  
 1315 1320 1325  
 Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln  
 1330 1335 1340  
 His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser  
 1345 1350 1355 1360  
 Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val  
 1365 1370 1375  
 His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His  
 1380 1385 1390  
 His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His  
 1395 1400 1405  
 Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr  
 1410 1415 1420  
 Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu  
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 Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val  
 1445 1450 1455  
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 1490 1495 1500  
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 Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile  
 1525 1530 1535  
 Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln Met Gln Val Thr Asp  
 1540 1545 1550  
 Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro  
 1555 1560 1565  
 Val Thr Gly Tyr Arg Val Thr Thr Pro Lys Asn Gly Pro Gly Pro  
 1570 1575 1580  
 Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu  
 1585 1590 1595 1600  
 Gly Leu Gln Pro Thr Val Glu Tyr Val Val Ser Val Tyr Ala Gln Asn  
 1605 1610 1615  
 Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr Ala Val Thr Asn Ile

## SEQUENCE LISTING 1657-2022.txt

1620 1625 1630  
 Asp Arg Pro Lys Gly Leu Ala Phe Thr Asp Val Asp Val Asp Ser Ile  
 1635 1640 1645  
 Lys Ile Ala Trp Glu Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val  
 1650 1655 1660  
 Thr Tyr Ser Ser Pro Glu Asp Gly Ile His Glu Leu Phe Pro Ala Pro  
 1665 1670 1675 1680  
 Asp Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly Leu Arg Pro Gly Ser  
 1685 1690 1695  
 Glu Tyr Thr Val Ser Val Val Ala Leu His Asp Asp Met Glu Ser Gln  
 1700 1705 1710  
 Pro Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu  
 1715 1720 1725  
 Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro  
 1730 1735 1740  
 Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu  
 1745 1750 1755 1760  
 Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser  
 1765 1770 1775  
 Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val  
 1780 1785 1790  
 Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val  
 1795 1800 1805  
 Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp  
 1810 1815 1820  
 Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr  
 1825 1830 1835 1840  
 Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro  
 1845 1850 1855  
 Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly  
 1860 1865 1870  
 Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp  
 1875 1880 1885  
 Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp  
 1890 1895 1900  
 Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu  
 1905 1910 1915 1920  
 Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys  
 1925 1930 1935  
 Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg  
 1940 1945 1950  
 Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu  
 1955 1960 1965  
 Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro  
 1970 1975 1980  
 Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro Gln Leu Val Thr Leu  
 1985 1990 1995 2000  
 Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr  
 2005 2010 2015  
 Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr Asp Thr Gly Asn  
 2020 2025 2030  
 Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln Pro Ser Val Gly Gln  
 2035 2040 2045  
 Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg Thr Thr Pro Pro Thr  
 2050 2055 2060  
 Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro Tyr Pro Pro Asn Val  
 2065 2070 2075 2080  
 Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser Trp Ala Pro Phe Gln  
 2085 2090 2095  
 Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro Val Gly Thr Asp Glu  
 2100 2105 2110  
 Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser Thr Ser Ala Thr Leu  
 2115 2120 2125  
 Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile Ile Val Glu Ala Leu  
 2130 2135 2140  
 Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu Val Val Thr Val Gly  
 2145 2150 2155 2160

## SEQUENCE LISTING 1657-2022.txt

Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr Asp Asp Ser Cys Phe  
 2165 2170 2175  
 Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp Glu Arg  
 2180 2185 2190  
 Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly  
 2195 2200 2205  
 Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly  
 2210 2215 2220  
 Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly  
 2225 2230 2235 2240  
 Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys  
 2245 2250 2255  
 Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His  
 2260 2265 2270  
 Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys  
 2275 2280 2285  
 Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg  
 2290 2295 2300  
 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn  
 2305 2310 2315 2320  
 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys  
 2325 2330 2335  
 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp  
 2340 2345 2350  
 Ser Arg Glu  
 2355

<210> 136  
 <211> 1366  
 <212> PRT  
 <213> Homo sapiens

<400> 136  
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 Leu Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Glu Thr Val Arg Lys  
 20 25 30  
 Gly Pro Ala Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly  
 35 40 45  
 Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro  
 50 55 60  
 Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln  
 65 70 75 80  
 Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met  
 85 90 95  
 Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly  
 100 105 110  
 Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro  
 115 120 125  
 Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp  
 130 135 140  
 Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly  
 145 150 155 160  
 Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe  
 165 170 175  
 Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro  
 180 185 190  
 Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly  
 195 200 205  
 Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg  
 210 215 220  
 Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val  
 225 230 235 240  
 Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly  
 245 250 255  
 Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn

## SEQUENCE LISTING 1657-2022.txt

260 265 270  
 Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro  
 275 280 285  
 Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly  
 290 295 300  
 Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala  
 305 310 315 320  
 Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala  
 325 330 335  
 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly  
 340 345 350  
 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro  
 355 360 365  
 Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn  
 370 375 380  
 Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Gly Leu Arg Gly  
 385 390 395 400  
 Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val  
 405 410 415  
 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg  
 420 425 430  
 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly  
 435 440 445  
 Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys  
 450 455 460  
 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile  
 465 470 475 480  
 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly  
 485 490 495  
 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His  
 500 505 510  
 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn  
 515 520 525  
 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly  
 530 535 540  
 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro  
 545 550 555 560  
 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His  
 565 570 575  
 Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly  
 580 585 590  
 Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser  
 595 600 605  
 Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro  
 610 615 620  
 Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly  
 625 630 635 640  
 Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu  
 645 650 655  
 Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp  
 660 665 670  
 Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly  
 675 680 685  
 Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro  
 690 695 700  
 Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala  
 705 710 715 720  
 Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly  
 725 730 735  
 Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val  
 740 745 750  
 Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn  
 755 760 765  
 Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Pro Pro Gly  
 770 775 780  
 Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro  
 785 790 795 800

## SEQUENCE LISTING 1657-2022.txt

Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu  
 805 810 815  
 Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly  
 820 825 830  
 Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro  
 835 840 845  
 Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln  
 850 855 860  
 Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly  
 865 870 875 880  
 Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro  
 885 890 895  
 Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val  
 900 905 910  
 Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly  
 915 920 925  
 Asn Pro Gly Asn Asp Gly Pro Gly Arg Asp Gly Gln Pro Gly His  
 930 935 940  
 Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala  
 945 950 955 960  
 Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly  
 965 970 975  
 Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala  
 980 985 990  
 Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys  
 995 1000 1005  
 Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly  
 1010 1015 1020  
 His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp  
 1025 1030 1035 1040  
 Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala  
 1045 1050 1055  
 Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly  
 1060 1065 1070  
 Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro  
 1075 1080 1085  
 Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser  
 1090 1095 1100  
 Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp  
 1105 1110 1115 1120  
 Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp  
 1125 1130 1135  
 Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro  
 1140 1145 1150  
 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu  
 1155 1160 1165  
 Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln  
 1170 1175 1180  
 Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly  
 1185 1190 1195 1200  
 Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp  
 1205 1210 1215  
 Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile  
 1220 1225 1230  
 Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys  
 1235 1240 1245  
 Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala  
 1250 1255 1260  
 Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp  
 1265 1270 1275 1280  
 Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn  
 1285 1290 1295  
 Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val  
 1300 1305 1310  
 Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile  
 1315 1320 1325  
 Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile

## SEQUENCE LISTING 1657-2022.txt

1330 1335 1340  
 Ala Pro Leu Asp Ile Gly Gly Ala Asp His Glu Phe Phe Val Asp Ile  
 1345 1350 1355 1360  
 Gly Pro Val Cys Phe Lys  
 1365

<210> 137  
 <211> 105  
 <212> PRT  
 <213> Homo sapiens

<400> 137  
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 20 25 30  
 Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala  
 35 40 45  
 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met  
 50 55 60  
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe  
 65 70 75 80  
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu  
 85 90 95  
 Lys Ala Val Pro Ser Gln Lys Arg Thr  
 100 105

<210> 138  
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 <212> PRT  
 <213> Homo sapiens

<400> 138  
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 20 25 30  
 Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn  
 35 40 45  
 Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg  
 50 55 60  
 Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser  
 65 70 75 80  
 Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met  
 85 90 95  
 Thr Ile Gly Phe Ile Leu Leu Leu Val Phe Gly Ser Val Thr Val Tyr  
 100 105 110  
 His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr  
 115 120 125

<210> 139  
 <211> 163  
 <212> PRT  
 <213> Homo sapiens

<400> 139  
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 20 25 30  
 Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly  
 35 40 45  
 Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys  
 50 55 60



## SEQUENCE LISTING 1657-2022.txt

Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His  
 65 70 75 80  
 Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys  
 85 90 95  
 Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg  
 100 105 110  
 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn  
 115 120 125  
 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys  
 130 135 140  
 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp  
 145 150 155 160  
 Ser Arg Glu

<210> 140  
 <211> 1466  
 <212> PRT  
 <213> Homo sapiens

<400> 140  
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 20 25 30  
 Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu  
 35 40 45  
 Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp  
 50 55 60  
 Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro  
 65 70 75 80  
 Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr  
 85 90 95  
 Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly  
 100 105 110  
 Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln  
 115 120 125  
 Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys  
 130 135 140  
 Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val  
 145 150 155 160  
 Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala  
 165 170 175  
 Gly Pro Pro Gly Pro Pro Gly Pro Gly Thr Ser Gly His Pro Gly  
 180 185 190  
 Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln  
 195 200 205  
 Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser  
 210 215 220  
 Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly  
 225 230 235 240  
 Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile  
 245 250 255  
 Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn  
 260 265 270  
 Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly  
 275 280 285  
 Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala  
 290 295 300  
 Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg  
 305 310 315 320  
 Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly  
 325 330 335  
 Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu  
 340 345 350  
 Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg  
 Page 127

## SEQUENCE LISTING 1657-2022.txt

355  
 Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly  
 370  
 Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro  
 385  
 Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro  
 405  
 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly  
 420  
 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu  
 435  
 Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp  
 450  
 Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly  
 465  
 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro  
 485  
 Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro  
 500  
 Gly Pro Ala Gly Pro Arg Gly Ala Gly Glu Pro Gly Arg Asp Gly  
 515  
 Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly  
 530  
 Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser  
 545  
 Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly  
 565  
 Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys  
 580  
 Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro  
 595  
 Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly  
 610  
 Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu  
 625  
 Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro  
 645  
 Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly  
 660  
 Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu  
 675  
 Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu  
 690  
 Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Gly Ala Ala Gly  
 705  
 Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser  
 725  
 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp  
 740  
 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly  
 755  
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala  
 770  
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg  
 785  
 Gly Glu Thr Gly Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly  
 805  
 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu  
 820  
 Lys Gly Glu Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser  
 835  
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly  
 850  
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu  
 865  
 Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser  
 885

## SEQUENCE LISTING 1657-2022.txt

Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly  
 900 905 910  
 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln  
 915 920 925  
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Gly Ala Pro  
 930 935 940  
 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly  
 945 950 955 960  
 Pro Pro Gly Met Pro Gly Pro Arg Gly Ser Pro Gly Pro Gln Gly Val  
 965 970 975  
 Lys Gly Glu Ser Gly Lys Pro Gly Ala Asn Gly Leu Ser Gly Glu Arg  
 980 985 990  
 Gly Pro Pro Gly Pro Gln Gly Leu Pro Gly Leu Ala Gly Thr Ala Gly  
 995 1000 1005  
 Glu Pro Gly Arg Asp Gly Asn Pro Gly Ser Asp Gly Leu Pro Gly Arg  
 1010 1015 1020  
 Asp Gly Ser Pro Gly Gly Lys Gly Asp Arg Gly Glu Asn Gly Ser Pro  
 1025 1030 1035 1040  
 Gly Ala Pro Gly Ala Pro Gly His Pro Gly Pro Pro Gly Pro Val Gly  
 1045 1050 1055  
 Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Ser Gly Pro Ala Gly Pro  
 1060 1065 1070  
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 1075 1080 1085  
 Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Arg Gly Ala Ala Gly  
 1090 1095 1100  
 Ile Lys Gly His Arg Gly Phe Pro Gly Asn Pro Gly Ala Pro Gly Ser  
 1105 1110 1115 1120  
 Pro Gly Pro Ala Gly Gln Gln Gly Ala Ile Gly Ser Pro Gly Pro Ala  
 1125 1130 1135  
 Gly Pro Arg Gly Pro Val Gly Pro Ser Gly Pro Pro Gly Lys Asp Gly  
 1140 1145 1150  
 Thr Ser Gly His Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg Gly Asn  
 1155 1160 1165  
 Arg Gly Glu Arg Gly Ser Glu Gly Ser Pro Gly His Pro Gly Gln Pro  
 1170 1175 1180  
 Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val  
 1185 1190 1195 1200  
 Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe  
 1205 1210 1215  
 Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp  
 1220 1225 1230  
 Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu  
 1235 1240 1245  
 Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp  
 1250 1255 1260  
 Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp  
 1265 1270 1275 1280  
 Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met  
 1285 1290 1295  
 Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg  
 1300 1305 1310  
 Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe  
 1315 1320 1325  
 Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu  
 1330 1335 1340  
 Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu  
 1345 1350 1355 1360  
 Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile  
 1365 1370 1375  
 Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu  
 1380 1385 1390  
 Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe  
 1395 1400 1405  
 Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp  
 1410 1415 1420  
 Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro

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1425          1430          1435          1440
Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe
          1445          1450          1455
Gly Val Asp Val Gly Pro Val Cys Phe Leu
          1460          1465

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[illegible]

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Ile	Gln	Asp	Ala	Ala	Ser	Lys	Asn	Glu	Asp	Gln	Glu	Met	Cys	His	Glu	
			20					25					30			
Phe	Gln	Ala	Phe	Met	Lys	Asn	Gly	Lys	Leu	Phe	Cys	Pro	Gln	Asp	Lys	
		35					40					45				
Lys	Phe	Phe	Gln	Ser	Leu	Asp	Gly	Ile	Met	Phe	Ile	Asn	Lys	Cys	Ala	
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Thr	Cys	Lys	Met	Ile	Leu	Glu	Lys	Glu	Ala	Lys	Ser	Gln	Lys	Arg	Ala	
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Arg	His	Leu	Ala	Arg	Ala	Pro	Lys	Ala	Thr	Ala	Pro	Thr	Glu	Leu	Asn	
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Cys	Asp	Asp	Phe	Lys	Lys	Gly	Glu	Arg	Asp	Gly	Asp	Phe	Ile	Cys	Pro	
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Asp	Tyr	Tyr	Glu	Ala	Val	Cys	Gly	Thr	Asp	Gly	Lys	Thr	Tyr	Asp	Asn	
		115					120					125				
Arg	Cys	Ala	Leu	Cys	Ala	Glu	Asn	Ala	Lys	Thr	Gly	Ser	Gln	Ile	Gly	
	130					135					140					
Val	Lys	Ser	Glu	Gly	Glu	Cys	Lys	Ser	Ser	Asn	Pro	Glu	Gln	Asp	Val	
145					150					155					160	
Cys	Ser	Ala	Phe	Arg	Pro	Phe	Val	Arg	Asp	Gly	Arg	Leu	Gly	Cys	Thr	
				165					170					175		

## SEQUENCE LISTING 1657-2022.txt

Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn  
 180 185 190  
 Lys Cys Ala Met Cys Ala Glu Leu Phe Leu Lys Glu Ala Glu Asn Ala  
 195 200 205  
 Lys Arg Glu Gly Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe  
 210 215 220  
 Cys Lys Glu Tyr Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr  
 225 230 235 240  
 Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn  
 245 250 255  
 Lys Cys Ala Leu Cys Ala Glu Ile Phe Lys Arg Arg Phe Ser Glu Glu  
 260 265 270  
 Asn Ser Lys Thr Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys  
 275 280 285  
 Val Lys Arg Glu Ile Val Lys Leu Cys Ser Gln Tyr Gln Asn Gln Ala  
 290 295 300  
 Lys Asn Gly Ile Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Arg Gly  
 305 310 315 320  
 Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Val Tyr  
 325 330 335  
 Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg  
 340 345 350  
 Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Asn  
 355 360 365  
 Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu  
 370 375 380  
 Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys  
 385 390 395 400  
 Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Lys Lys Lys  
 405 410 415  
 Lys Glu Gly Glu Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser  
 420 425 430  
 Phe Glu Glu Leu Cys Ser Glu Tyr Arg Lys Ser Arg Lys Asn Gly Arg  
 435 440 445  
 Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys  
 450 455 460  
 Met His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu  
 465 470 475 480  
 Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys  
 485 490 495  
 Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg  
 500 505 510  
 Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys  
 515 520 525  
 Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Glu Glu Lys Lys  
 530 535 540  
 Asn Asp Lys Glu Glu Lys Gly Lys Val Glu Ala Glu Lys Val Lys Arg  
 545 550 555 560  
 Glu Ala Val Gln Glu Leu Cys Ser Glu Tyr Arg His Tyr Val Arg Asn  
 565 570 575  
 Gly Arg Leu Pro Cys Thr Arg Glu Asn Asp Pro Ile Glu Gly Leu Asp  
 580 585 590  
 Gly Lys Ile His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln  
 595 600 605  
 Gln Glu Ala Lys Glu Lys Glu Arg Ala Glu Pro Arg Ala Lys Val Lys  
 610 615 620  
 Arg Glu Ala Glu Lys Glu Thr Cys Asp Glu Phe Arg Arg Leu Leu Gln  
 625 630 635 640  
 Asn Gly Lys Leu Phe Cys Thr Arg Glu Asn Asp Pro Val Arg Gly Pro  
 645 650 655  
 Asp Gly Lys Thr His Gly Asn Lys Cys Ala Met Cys Lys Ala Val Phe  
 660 665 670  
 Gln Lys Glu Asn Glu Glu Arg Lys Arg Lys Glu Glu Glu Asp Gln Arg  
 675 680 685  
 Asn Ala Ala Gly His Gly Ser Ser Gly Gly Gly Gly Asn Thr Gln  
 690 695 700  
 Asp Glu Cys Ala Glu Tyr Gln Glu Gln Met Lys Asn Gly Arg Leu Ser

## SEQUENCE LISTING 1657-2022.txt

705 Cys Thr Arg Glu Ser 710 Asp Pro Val Arg Asp Ala Asp Gly Lys Ser Tyr  
 725 Met Cys Lys Ala Lys Leu Glu Arg Glu Ala Glu  
 740 Thr Ser Arg Ser Arg Ser Asn Gly Thr Gly Ser Glu  
 755 Lys Asp Thr Cys Asp Glu Phe Arg Ser Gln Met Lys Asn Gly  
 770 Lys Leu Ile Cys Thr Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly  
 785 Lys Thr His Gly Asn Lys Cys Thr Met Cys Lys Glu Lys Leu Glu Arg  
 805 Glu Ala Ala Glu Lys Lys Lys Lys Glu Asp Glu Asp Arg Ser Asn Thr  
 820 Gly Glu Arg Ser Asn Thr Gly Glu Arg Ser Asn Asp Lys Glu Asp Leu  
 835 Cys Arg Glu Phe Arg Ser Met Gln Arg Asn Gly Lys Leu Ile Cys Thr  
 850 Arg Glu Asn Asn Pro Val Arg Gly Pro Tyr Gly Lys Met His Ile Asn  
 865 Lys Cys Ala Met Cys Gln Ser Ile Phe Asp Arg Glu Ala Asn Glu Arg  
 885 Lys Lys Lys Asp Glu Glu Lys Ser Ser Lys Pro Ser Asn Asn Ala  
 900 Lys Asp Glu Cys Ser Glu Phe Arg Asn Tyr Ile Arg Asn Asn Glu Leu  
 915 Ile Cys Pro Arg Glu Asn Asp Pro Val His Gly Ala Asp Gly Lys Phe  
 930 Tyr Thr Asn Lys Cys Tyr Met Cys Arg Ala Val Phe Leu Thr Glu Ala  
 945 Leu Glu Arg Ala Lys Leu Gln Glu Lys Pro Ser His Val Arg Ala Ser  
 965 Gln Glu Glu Asp Ser Pro Asp Ser Phe Ser Ser Leu Asp Ser Glu Met  
 980 Cys Lys Asp Tyr Arg Val Leu Pro Arg Ile Gly Tyr Leu Cys Pro Lys  
 995 Asp Leu Lys Pro Val Cys Gly Asp Asp Gly Gln Thr Tyr Asn Asn Pro  
 1010 Cys Met Leu Cys His Glu Asn Leu Ile Arg Gln Thr Asn Thr His Ile  
 1025 Arg Ser Thr Gly Lys Cys Glu Glu Ser Ser Thr Pro Gly Thr Thr Ala  
 1045 Ala Ser Met Pro Pro Ser Asp Glu 1050 1055  
 1060

<210> 143  
 <211> 967  
 <212> PRT  
 <213> Homo sapiens

<400> 143  
 Met Ala Lys Gly Phe Tyr Ile Ser Lys Ser Leu Gly Ile Leu Gly Ile  
 1 5 10 15  
 Leu Leu Gly Val Ala Ala Val Cys Thr Ile Ile Ala Leu Ser Val Val  
 20 25 30  
 Tyr Ser Gln Glu Lys Asn Lys Asn Ala Asn Ser Ser Pro Val Ala Ser  
 35 40 45  
 Thr Thr Pro Ser Ala Ser Ala Thr Thr Asn Pro Ala Ser Ala Thr Thr  
 50 55 60  
 Leu Asp Gln Ser Lys Ala Trp Asn Arg Tyr Arg Leu Pro Asn Thr Leu  
 65 70 75 80  
 Lys Pro Asp Ser Tyr Gln Val Thr Leu Arg Pro Tyr Leu Thr Pro Asn  
 85 90 95  
 Asp Arg Gly Leu Tyr Val Phe Lys Gly Ser Ser Thr Val Arg Phe Thr  
 100 105 110

## SEQUENCE LISTING 1657-2022.txt

Cys Lys Glu Ala Thr Asp Val Ile Ile Ile His Ser Lys Lys Leu Asn  
 Tyr Thr 115 Ser Gln Gly His Arg Val Val Leu Arg Gly Val Gly Gly  
 Ser 130 Gln Pro Pro Asp Ile Asp Lys Thr Glu Leu Val Glu Pro Thr Glu  
 145 Tyr Leu Val Val His Leu Lys Gly Ser Leu Val Lys Asp Ser Gln Tyr  
 Glu Met Asp Ser 165 Phe Glu Gly Glu 170 Ala Asp Asp Leu Ala Gly  
 Phe Tyr Arg Ser Glu Tyr Met Glu Gly Asn Val Arg Lys Val Val Ala  
 Thr Thr 195 Met Gln Ala Ala Asp Ala Arg Lys Ser Phe Pro Cys Phe  
 210 Asp Glu Pro Ala Met Lys Ala Glu Phe Asn Ile Thr Leu Ile His Pro  
 225 Lys Asp Leu Thr Ala 230 Ser Asn Met Leu 235 Pro Lys Gly Pro Ser Thr  
 Pro Leu Pro Glu Asp Pro Asn Trp Asn Val Thr Glu Phe His Thr Thr  
 Pro Lys Met 260 Ser Thr Tyr Leu Leu 265 Phe Ile Val Ser Glu Phe Asp  
 Tyr Val Glu Lys Gln Ala Ser Asn Gly Val Leu Ile Arg Ile Trp Ala  
 Arg 290 Pro Ser Ala Ile Ala 310 Gly His Gly Asp Tyr Ala Leu Asn Val  
 305 Thr Gly Pro Ile Leu Asn Phe Phe Ala Gly His Tyr Asp Thr Pro Tyr  
 Pro Leu Pro Lys 325 Ser Asp Gln Ile Gly 330 Leu Pro Asp Phe Asn Ala Gly  
 Ala Met Glu Asn Trp Gly Leu Val Thr Tyr Arg Glu Asn Ser Leu Leu  
 Phe Asp 355 Pro Leu Ser Ser Ser 360 Ser Ser Asn Lys Glu Arg Val Val Thr  
 Val 370 Ile Ala His Glu Leu Ala His Gln Trp Phe Gly Asn Leu Val Thr  
 385 Ile Glu Trp Trp Asn 390 Asp Leu Trp Leu Asn 410 Glu Gly Phe Ala Ser Tyr  
 Val Glu Tyr Leu Gly Ala Asp Tyr Ala Glu Pro Thr Trp Asn Leu Lys  
 Asp Leu Met 420 Val Leu Asn Asp Val Tyr Arg Val Met Ala Val Asp Ala  
 Leu Ala Ser Ser His Pro Leu Ser Thr Pro Ala Ser Glu Ile Asn Thr  
 Pro 450 Ala Gln Ile Ser Glu 455 Leu Phe Asp Ala Ile Ser Tyr Ser Lys Gly  
 465 Ala Ser Val Leu Arg Met Leu Ser Ser Phe Leu Ser Glu Asp Val Phe  
 Lys Gln Gly Leu 485 Ala Ser Tyr Leu His 505 Thr Phe Ala Tyr Gln Asn Thr  
 Ile Tyr Leu Asn Leu Trp Asp His 520 Leu Gln Glu Ala Val Asn Asn Arg  
 Ser Ile 515 Gln Leu Pro Thr Thr 535 Val Arg Asp Ile Met Asn Arg Trp Thr  
 Leu 530 Gln Met Gly Phe Pro Val Ile Thr Val Asp Thr Ser Thr Gly Thr  
 545 Leu Ser Gln Glu His 550 Phe Leu Leu Asp Pro Asp Ser Asn Val Thr Arg  
 Pro Ser Glu Phe 565 Asn Tyr Val Trp Ile Val Pro Ile Thr Ser Ile Arg  
 Asp Gly Arg 580 Gln Gln Asp Tyr 585 Trp Leu Ile Asp Val Arg Ala Gln  
 Asn Asp 595 Leu Phe Ser Thr Ser Gly Asn Glu Trp Val Leu Leu Asn Leu  
 610 Asn Val Thr Gly Tyr Tyr 615 Arg Val Asn Tyr Asp Glu Glu Asn Trp Arg  
 625 Lys Ile Gln Thr Gln Leu Gln Arg Asp His Ser Ala Ile Pro Val Ile

## SEQUENCE LISTING 1657-2022.txt

```

        645          650          655
Asn Arg Ala Gln Ile Ile Asn Asp Ala Phe Asn Leu Ala Ser Ala His
Lys Val Pro 660 Thr Leu Ala Leu 665 Asn Asn Thr Leu Phe 670 Leu Ile Glu
Glu Arg Gln Tyr Met Pro Trp 680 Glu Ala Ala Leu Ser Ser Leu Ser Tyr
Phe 690 Lys Leu Met Phe Asp 695 Arg Ser Glu Val Tyr Gly Pro Met Lys Asn
705 710 715 720
Tyr Leu Lys Lys Gln Val Thr Pro Leu Phe Ile His Phe Arg Asn Asn
725 730 735
Thr Asn Asn Trp Arg Glu Ile Pro Glu Asn Leu Met Asp Gln Tyr Ser
740 745 750
Glu Val Asn Ala Ile Ser Thr Ala Cys Ser Asn Gly Val Pro Glu Cys
755 760 765
Glu Glu Met Val Ser Gly Leu Phe Lys Gln Trp Met Glu Asn Pro Asn
770 775 780
Asn Asn Pro Ile His Pro Asn Leu Arg Ser Thr Val Tyr Cys Asn Ala
785 790 795 800
Ile Ala Gln Gly Gly Glu Glu Glu Trp Asp Phe Ala Trp Glu Gln Phe
805 810 815
Arg Asn Ala Thr Leu Val Asn Glu Ala Asp Lys Leu Arg Ala Ala Leu
820 825 830
Ala Cys Ser Lys Glu Leu Trp Ile Leu Asn Arg Tyr Leu Ser Tyr Thr
835 840 845
Leu Asn Pro Asp Leu Ile Arg Lys Gln Asp Ala Thr Ser Thr Ile Ile
850 855 860
Ser Ile Thr Asn Asn Val Ile Gly Gln Gly Leu Val Trp Asp Phe Val
865 870 875 880
Gln Ser Asn Trp Lys Lys Leu Phe Asn Asp Tyr Gly Gly Gly Ser Phe
885 890 895
Ser Phe Ser Asn Leu Ile Gln Ala Val Thr Arg Arg Phe Ser Thr Glu
900 905 910
Tyr Glu Leu Gln Gln Leu Glu Gln Phe Lys Lys Asp Asn Glu Glu Thr
915 920 925
Gly Phe Gly Ser Gly Thr Arg Ala Leu Glu Gln Ala Leu Glu Lys Thr
930 935 940
Lys Ala Asn Ile Lys Trp Val Lys Glu Asn Lys Glu Val Val Leu Gln
945 950 955 960
Trp Phe Thr Glu Asn Ser Lys
965

```

<210> 144  
 <211> 261  
 <212> PRT  
 <213> Homo sapiens

```

<400> 144
Met Ser Gly Glu Ile Ala Met Cys Glu Pro Glu Phe Gly Asn Asp Lys
1 5 10 15
Ala Arg Glu Pro Ser Val Gly Gly Arg Trp Arg Val Ser Trp Tyr Glu
20 25 30
Arg Phe Val Gln Pro Cys Leu Val Glu Leu Leu Gly Ser Ala Leu Phe
35 40 45
Ile Phe Ile Gly Cys Leu Ser Val Ile Glu Asn Gly Thr Asp Thr Gly
50 55 60
Leu Leu Gln Pro Ala Leu Ala His Gly Leu Ala Leu Gly Leu Val Ile
65 70 75 80
Ala Thr Leu Gly Asn Ile Ser Gly Gly His Phe Asn Pro Ala Val Ser
85 90 95
Leu Ala Ala Met Leu Ile Gly Gly Leu Asn Leu Val Met Leu Leu Pro
100 105 110
Tyr Trp Val Ser Gln Leu Leu Gly Gly Met Leu Gly Ala Ala Leu Ala
115 120 125
Lys Val Val Ser Pro Glu Glu Arg Phe Trp Asn Ala Ser Gly Ala Ala
130 135 140

```



## SEQUENCE LISTING 1657-2022.txt

Phe Val Thr Val Gln Glu Gln Gly Gln Val Ala Gly Ala Leu Val Ala  
 145 150 155 160  
 Glu Ile Ile Leu Thr Leu Leu Ala Leu Ala Val Cys Met Gly Ala  
 165 170 175  
 Ile Asn Glu Lys Thr Lys Gly Pro Leu Ala Pro Phe Ser Ile Gly Phe  
 180 185 190  
 Ala Val Thr Val Asp Ile Leu Ala Gly Gly Pro Val Ser Gly Gly Cys  
 195 200 205  
 Met Asn Pro Ala Arg Ala Phe Gly Pro Ala Val Val Ala Asn His Trp  
 210 215 220  
 Asn Phe His Trp Ile Tyr Trp Leu Gly Pro Leu Leu Ala Gly Leu Leu  
 225 230 235 240  
 Val Gly Leu Leu Ile Arg Cys Phe Ile Gly Asp Gly Lys Thr Arg Leu  
 245 250 255  
 Ile Leu Lys Ala Arg  
 260

<210> 145  
 <211> 112  
 <212> PRT  
 <213> Homo sapiens

<400> 145  
 Met Gly Cys Arg Ala Ala Ser Gly Leu Leu Pro Gly Val Ala Val Val  
 1 5 10 15  
 Leu Leu Leu Leu Leu Gln Ser Thr Gln Ser Val Tyr Ile Gln Tyr Gln  
 20 25 30  
 Gly Phe Arg Val Gln Leu Glu Ser Met Lys Lys Leu Ser Asp Leu Glu  
 35 40 45  
 Ala Gln Trp Ala Pro Ser Pro Arg Leu Gln Ala Gln Ser Leu Leu Pro  
 50 55 60  
 Ala Val Cys His His Pro Ala Leu Pro Gln Asp Leu Gln Pro Val Cys  
 65 70 75 80  
 Ala Ser Gln Glu Ala Ser Ser Ile Phe Lys Thr Leu Arg Thr Ile Ala  
 85 90 95  
 Asn Asp Asp Cys Glu Leu Cys Val Asn Val Ala Cys Thr Gly Cys Leu  
 100 105 110

<210> 146  
 <211> 917  
 <212> PRT  
 <213> Homo sapiens

<400> 146  
 Met Gly Leu Phe Arg Gly Phe Val Phe Leu Leu Val Leu Cys Leu Leu  
 1 5 10 15  
 His Gln Ser Asn Thr Ser Phe Ile Lys Leu Asn Asn Asn Gly Phe Glu  
 20 25 30  
 Asp Ile Val Ile Val Ile Asp Pro Ser Val Pro Glu Asp Glu Lys Ile  
 35 40 45  
 Ile Glu Gln Ile Glu Asp Met Val Thr Thr Ala Ser Thr Tyr Leu Phe  
 50 55 60  
 Glu Ala Thr Glu Lys Arg Phe Phe Phe Lys Asn Val Ser Ile Leu Ile  
 65 70 75 80  
 Pro Glu Asn Trp Lys Glu Asn Pro Gln Tyr Lys Arg Pro Lys His Glu  
 85 90 95  
 Asn His Lys His Ala Asp Val Ile Val Ala Pro Pro Thr Leu Pro Gly  
 100 105 110  
 Arg Asp Glu Pro Tyr Thr Lys Gln Phe Thr Glu Cys Gly Glu Lys Gly  
 115 120 125  
 Glu Tyr Ile His Phe Thr Pro Asp Leu Leu Leu Gly Lys Lys Gln Asn  
 130 135 140  
 Glu Tyr Gly Pro Pro Gly Lys Leu Phe Val His Glu Trp Ala His Leu  
 145 150 155 160  
 Arg Trp Gly Val Phe Asp Glu Tyr Asn Glu Asp Gln Pro Phe Tyr Arg

## SEQUENCE LISTING 1657-2022.txt

```

165      170      175
Ala Lys Ser Lys Lys Ile Glu Ala Thr Arg Cys Ser Ala Gly Ile Ser
180      185      190
Gly Arg Asn Arg Val Tyr Lys Cys Gln Gly Gly Ser Cys Leu Ser Arg
195      200      205
Ala Cys Arg Ile Asp Ser Thr Thr Lys Leu Tyr Gly Lys Asp Cys Gln
210      215      220
Phe Phe Pro Asp Lys Val Gln Thr Glu Lys Ala Ser Ile Met Phe Met
225      230      235
Gln Ser Ile Asp Ser Val Val Glu Phe Cys Asn Glu Lys Thr His Asn
240      245      250
Gln Glu Ala Pro Ser Leu Gln Asn Ile Lys Cys Asn Phe Arg Ser Thr
255      260      265
Trp Glu Val Ile Ser Asn Ser Glu Asp Phe Lys Asn Thr Ile Pro Met
270      275      280
Val Thr Pro Pro Pro Pro Val Phe Ser Leu Leu Lys Ile Arg Gln
285      290      295
Arg Ile Val Cys Leu Val Leu Asp Lys Ser Gly Ser Met Gly Gly Lys
300      305      310
Asp Arg Leu Asn Arg Met Asn Gln Ala Ala Lys His Phe Leu Leu Gln
315      320      325
Thr Val Glu Asn Gly Ser Trp Val Gly Met Val His Phe Asp Ser Thr
330      335      340
Ala Thr Ile Val Asn Lys Leu Ile Gln Ile Lys Ser Ser Asp Glu Arg
345      350      355
Asn Thr Leu Met Ala Gly Leu Pro Thr Tyr Pro Leu Gly Gly Thr Ser
360      365      370
Ile Cys Ser Gly Ile Lys Tyr Ala Phe Gln Val Ile Gly Glu Leu His
375      380      385
Ser Gln Leu Asp Gly Ser Glu Val Leu Leu Leu Thr Asp Gly Glu Asp
390      395      400
Asn Thr Ala Ser Ser Cys Ile Asp Glu Val Lys Gln Ser Gly Ala Ile
405      410      415
Val His Phe Ile Ala Leu Gly Arg Ala Ala Asp Glu Ala Val Ile Glu
420      425      430
Met Ser Lys Ile Thr Gly Gly Ser His Phe Tyr Val Ser Asp Glu Ala
435      440      445
Gln Asn Asn Gly Leu Ile Asp Ala Phe Gly Ala Leu Thr Ser Gly Asn
450      455      460
Thr Asp Leu Ser Gln Lys Ser Leu Gln Leu Glu Ser Lys Gly Leu Thr
465      470      475
Leu Asn Ser Asn Ala Trp Met Asn Asp Thr Val Ile Ile Asp Ser Thr
480      485      490
Val Gly Lys Asp Thr Phe Phe Leu Ile Thr Trp Asn Ser Leu Pro Pro
495      500      505
Ser Ile Ser Leu Trp Asp Pro Ser Gly Thr Ile Met Glu Asn Phe Thr
510      515      520
Val Asp Ala Thr Ser Lys Met Ala Tyr Leu Ser Ile Pro Gly Thr Ala
525      530      535
Lys Val Gly Thr Trp Ala Tyr Asn Leu Gln Ala Lys Ala Asn Pro Glu
540      545      550
Thr Leu Thr Ile Thr Val Thr Ser Arg Ala Ala Asn Ser Ser Val Pro
555      560      565
Pro Ile Thr Val Asn Ala Lys Met Asn Lys Asp Val Asn Ser Phe Pro
570      575      580
Ser Pro Met Ile Val Tyr Ala Glu Ile Leu Gln Gly Tyr Val Pro Val
585      590      595
Leu Gly Ala Asn Val Thr Ala Phe Ile Glu Ser Gln Asn Gly His Thr
600      605      610
Glu Val Leu Glu Leu Leu Asp Asn Gly Ala Gly Ala Asp Ser Phe Lys
615      620      625
Asn Asp Gly Val Tyr Ser Arg Tyr Phe Thr Ala Tyr Thr Glu Asn Gly
630      635      640
Arg Tyr Ser Leu Lys Val Arg Ala His Gly Gly Ala Asn Thr Ala Arg
645      650      655
Leu Lys Leu Arg Pro Pro Leu Asn Arg Ala Ala Tyr Ile Pro Gly Trp
660      665      670
675      680      685
690      695      700

```

## SEQUENCE LISTING 1657-2022.txt

```

val Val Asn Gly Glu Ile Glu Ala Asn Pro Pro Arg Pro Glu Ile Asp
705 710 715 720
Glu Asp Thr Gln Thr Leu Glu Asp Phe Ser Arg Thr Ala Ser Gly
725 730 735
Gly Ala Phe Val Val Ser Gln Val Pro Ser Leu Pro Leu Pro Asp Gln
740 745 750
Tyr Pro Pro Ser Gln Ile Thr Asp Leu Asp Ala Thr Val His Glu Asp
755 760 765
Lys Ile Ile Leu Thr Trp Thr Ala Pro Gly Asp Asn Phe Asp Val Gly
770 775 780
Lys Val Gln Arg Tyr Ile Ile Arg Ile Ser Ala Ser Ile Leu Asp Leu
785 790 795 800
Arg Asp Ser Phe Asp Asp Ala Leu Gln Val Asn Thr Thr Asp Leu Ser
805 810 815
Pro Lys Glu Ala Asn Ser Lys Glu Ser Phe Ala Phe Lys Pro Glu Asn
820 825 830
Ile Ser Glu Glu Asn Ala Thr His Ile Phe Ile Ala Ile Lys Ser Ile
835 840 845
Asp Lys Ser Asn Leu Thr Ser Lys Val Ser Asn Ile Ala Gln Val Thr
850 855 860
Leu Phe Ile Pro Gln Ala Asn Pro Asp Asp Ile Asp Pro Thr Pro Thr
865 870 875 880
Pro Thr Pro Thr Pro Asp Lys Ser His Asn Ser Gly Val Asn Ile Ser
885 890 895
Thr Leu Val Leu Ser Val Ile Gly Ser Val Val Ile Val Asn Phe Ile
900 905 910
Leu Ser Thr Thr Ile
915

```

<210> 147  
 <211> 437  
 <212> PRT  
 <213> Homo sapiens

```

<400> 147
Met Ser Ala Val Leu Leu Leu Ala Leu Leu Gly Phe Ile Leu Pro Leu
1 5 10 15
Pro Gly Val Gln Ala Leu Leu Cys Gln Phe Gly Thr Val Gln His Val
20 25 30
Trp Lys Val Ser Asp Leu Pro Arg Gln Trp Thr Pro Lys Asn Thr Ser
35 40 45
Cys Asp Ser Gly Leu Gly Cys Gln Asp Thr Leu Met Leu Ile Glu Ser
50 55 60
Gly Pro Gln Val Ser Leu Val Leu Ser Lys Gly Cys Thr Glu Ala Lys
65 70 75 80
Asp Gln Glu Pro Arg Val Thr Glu His Arg Met Gly Pro Gly Leu Ser
85 90 95
Leu Ile Ser Tyr Thr Phe Val Cys Arg Gln Glu Asp Phe Cys Asn Asn
100 105 110
Leu Val Asn Ser Leu Pro Leu Trp Ala Pro Gln Pro Pro Ala Asp Pro
115 120 125
Gly Ser Leu Arg Cys Pro Val Cys Leu Ser Met Glu Gly Cys Leu Glu
130 135 140
Gly Thr Thr Glu Glu Ile Cys Pro Lys Gly Thr Thr His Cys Tyr Asp
145 150 155 160
Gly Leu Leu Arg Leu Arg Gly Gly Gly Ile Phe Ser Asn Leu Arg Val
165 170 175
Gln Gly Cys Met Pro Gln Pro Gly Cys Asn Leu Leu Asn Gly Thr Gln
180 185 190
Glu Ile Gly Pro Val Gly Met Thr Glu Asn Cys Asn Arg Lys Asp Phe
195 200 205
Leu Thr Cys His Arg Gly Thr Thr Ile Met Thr His Gly Asn Leu Ala
210 215 220
Gln Glu Pro Thr Asp Trp Thr Thr Ser Asn Thr Glu Met Cys Glu Val
225 230 235 240
Gly Gln Val Cys Gln Glu Thr Leu Leu Leu Ile Asp Val Gly Leu Thr

```

## SEQUENCE LISTING 1657-2022.txt

```

                245                250                255
Ser Thr Leu Val Gly Thr Lys Gly Cys Ser Thr Val Gly Ala Gln Asn
                260                265                270
Ser Gln Lys Thr Thr Ile His Ser Ala Pro Pro Gly Val Leu Val Ala
                275                280                285
Ser Tyr Thr His Phe Cys Ser Ser Asp Leu Cys Asn Ser Ala Ser Ser
                290                295                300
Ser Ser Val Leu Leu Asn Ser Leu Pro Pro Gln Ala Ala Pro Val Pro
305                310                315
Gly Asp Arg Gln Cys Pro Thr Cys Val Gln Pro Leu Gly Thr Cys Ser
                325                330                335
Ser Gly Ser Pro Arg Met Thr Cys Pro Arg Gly Ala Thr His Cys Tyr
                340                345                350
Asp Gly Tyr Ile His Leu Ser Gly Gly Gly Leu Ser Thr Lys Met Ser
355                360                365
Ile Gln Gly Cys Val Ala Gln Pro Ser Ser Phe Leu Leu Asn His Thr
370                375                380
Arg Gln Ile Gly Ile Phe Ser Ala Arg Glu Lys Arg Asp Val Gln Pro
385                390                395
Pro Ala Ser Gln His Glu Gly Gly Gly Ala Glu Gly Leu Glu Ser Leu
400                405                410                415
Thr Trp Gly Val Gly Leu Ala Leu Ala Pro Ala Leu Trp Trp Gly Val
420                425                430
Val Cys Pro Ser Cys
435

```

<210> 148  
 <211> 452  
 <212> PRT  
 <213> Homo sapiens

```

<400> 148
Met Leu Cys Gly Arg Pro Arg Ser Ser Ser Asp Asn Arg Asn Phe Leu
1      5      10      15
Arg Glu Arg Ala Gly Leu Ser Ser Ala Val Gln Thr Arg Ile Gly
20      25      30
Asn Ser Ala Ala Ser Arg Arg Ser Pro Ala Ala Arg Pro Pro Val Pro
35      40      45
Ala Pro Pro Ala Leu Pro Arg Gly Arg Pro Gly Thr Glu Gly Ser Thr
50      55      60
Ser Leu Ser Ala Pro Ala Val Leu Val Val Ala Val Ala Val Val Val
65      70      75      80
Val Val Val Ser Ala Val Ala Trp Ala Met Ala Asn Tyr Ile His Val
85      90      95
Pro Pro Gly Ser Pro Glu Val Pro Lys Leu Asn Val Thr Val Gln Asp
100     105     110
Gln Glu Glu His Arg Cys Arg Glu Gly Ala Leu Ser Leu Leu Gln His
115     120     125
Leu Arg Pro His Trp Asp Pro Gln Glu Val Thr Leu Gln Leu Phe Thr
130     135     140
Asp Gly Ile Thr Asn Lys Leu Ile Gly Cys Tyr Val Gly Asn Thr Met
145     150     155     160
Glu Asp Val Val Leu Val Arg Ile Tyr Gly Asn Lys Thr Glu Leu Leu
165     170     175
Val Asp Arg Asp Glu Glu Val Lys Ser Phe Arg Val Leu Gln Ala His
180     185     190
Gly Cys Ala Pro Gln Leu Tyr Cys Thr Phe Asn Asn Gly Leu Cys Tyr
195     200     205
Glu Phe Ile Gln Gly Glu Ala Leu Asp Pro Lys His Val Cys Asn Pro
210     215     220
Ala Ile Phe Arg Leu Ile Ala Arg Gln Leu Ala Lys Ile His Ala Ile
225     230     235     240
His Ala His Asn Gly Trp Ile Pro Lys Ser Asn Leu Trp Leu Lys Met
245     250     255
Gly Lys Tyr Phe Ser Leu Ile Pro Thr Gly Phe Ala Asp Glu Asp Ile
260     265     270

```

## SEQUENCE LISTING 1657-2022.txt

Asn Lys Arg Phe Leu Ser Asp Ile Pro Ser Ser Gln Ile Leu Gln Glu  
 275 280 285  
 Glu Met Thr Trp Met Lys Glu Ile Leu Ser Asn Leu Gly Ser Pro Val  
 290 295 300  
 Val Leu Cys His Asn Asp Leu Leu Cys Lys Asn Ile Ile Tyr Asn Glu  
 305 310 315 320  
 Lys Gln Gly Asp Val Gln Phe Ile Asp Tyr Glu Tyr Ser Gly Tyr Asn  
 325 330 335  
 Tyr Leu Ala Tyr Asp Ile Gly Asn His Phe Asn Glu Phe Ala Gly Val  
 340 345 350  
 Ser Asp Val Asp Tyr Ser Leu Tyr Pro Asp Arg Glu Leu Gln Ser Gln  
 355 360 365  
 Trp Leu Arg Ala Tyr Leu Glu Ala Tyr Lys Glu Phe Lys Gly Phe Gly  
 370 375 380  
 Thr Glu Val Thr Glu Lys Glu Val Glu Ile Leu Phe Ile Gln Val Asn  
 385 390 395 400  
 Gln Phe Ala Leu Ala Ser His Phe Phe Trp Gly Leu Trp Ala Leu Ile  
 405 410 415  
 Gln Ala Lys Tyr Ser Thr Ile Glu Phe Asp Phe Leu Gly Tyr Ala Ile  
 420 425 430  
 Val Arg Phe Asn Gln Tyr Phe Lys Met Lys Pro Glu Val Thr Ala Leu  
 435 440 445  
 Lys Val Pro Glu  
 450

<210> 149  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 149  
 Met Gly Ser Leu Gly Ser Lys Asn Pro Gln Thr Lys Gln Ala Gln Val  
 1 5 10 15  
 Leu Leu Leu Gly Leu Asp Ser Ala Gly Lys Ser Thr Leu Leu Tyr Lys  
 20 25 30  
 Leu Lys Leu Ala Lys Asp Ile Thr Thr Ile Pro Thr Ile Gly Phe Asn  
 35 40 45  
 Val Glu Met Ile Glu Leu Glu Arg Asn Leu Ser Leu Thr Val Trp Asp  
 50 55 60  
 Val Gly Gly Gln Glu Lys Met Arg Thr Val Trp Gly Cys Tyr Cys Glu  
 65 70 75 80  
 Asn Thr Asp Gly Leu Val Tyr Val Val Asp Ser Thr Asp Lys Gln Arg  
 85 90 95  
 Leu Glu Glu Ser Gln Arg Gln Phe Glu His Ile Leu Lys Asn Glu His  
 100 105 110  
 Ile Lys Asn Val Pro Val Val Leu Leu Ala Asn Lys Gln Asp Met Pro  
 115 120 125  
 Gly Ala Leu Thr Ala Glu Asp Ile Thr Arg Met Phe Lys Val Lys Lys  
 130 135 140  
 Leu Cys Ser Asp Arg Asn Trp Tyr Val Gln Pro Cys Cys Ala Leu Thr  
 145 150 155 160  
 Gly Glu Gly Leu Ala Gln Gly Phe Arg Lys Leu Thr Gly Phe Val Lys  
 165 170 175  
 Ser His Met Lys Ser Arg Gly Asp Thr Leu Ala Phe Phe Lys Gln Asn  
 180 185 190

<210> 150  
 <211> 530  
 <212> PRT  
 <213> Homo sapiens

<400> 150  
 Met Ser Leu Lys Trp Thr Ser Val Phe Leu Leu Ile Gln Leu Ser Cys  
 1 5 10 15  
 Tyr Phe Ser Ser Gly Ser Cys Gly Lys Val Leu Val Trp Pro Thr Glu

## SEQUENCE LISTING 1657-2022.txt

```

      20      25      30
Tyr Ser His Trp Ile Asn Met Lys Thr Ile Leu Glu Glu Leu Val Gln
      35      40      45
Arg Gly His Glu Val Thr Val Leu Thr Ser Ser Ala Ser Thr Leu Val
      50      55      60
Asn Ala Ser Lys Ser Ser Ala Ile Lys Leu Glu Val Tyr Pro Thr Ser
      65      70      75      80
Leu Thr Lys Asn Asp Leu Glu Asp Ser Leu Leu Lys Ile Leu Asp Arg
      85      90      95
Trp Ile Tyr Gly Val Ser Lys Asn Thr Phe Trp Ser Tyr Phe Ser Gln
      100      105      110
Leu Gln Glu Leu Cys Trp Glu Tyr Tyr Asp Tyr Ser Asn Lys Leu Cys
      115      120      125
Lys Asp Ala Val Leu Asn Lys Lys Leu Met Met Lys Leu Gln Glu Ser
      130      135      140
Lys Phe Asp Val Ile Leu Ala Asp Ala Leu Asn Pro Cys Gly Glu Leu
      145      150      155      160
Leu Ala Glu Leu Phe Asn Ile Pro Phe Leu Tyr Ser Leu Arg Phe Ser
      165      170      175
Val Gly Tyr Thr Phe Glu Lys Asn Gly Gly Phe Leu Phe Pro Pro
      180      185      190
Ser Tyr Val Pro Val Val Met Ser Glu Leu Ser Asp Gln Met Ile Phe
      195      200      205
Met Glu Arg Ile Lys Asn Met Ile His Met Leu Tyr Phe Asp Phe Trp
      210      215      220
Phe Gln Ile Tyr Asp Leu Lys Lys Trp Asp Gln Phe Tyr Ser Glu Val
      225      230      235      240
Leu Gly Arg Pro Thr Thr Leu Phe Glu Thr Met Gly Lys Ala Glu Met
      245      250      255
Trp Leu Ile Arg Thr Tyr Trp Asp Phe Glu Phe Pro Arg Pro Phe Leu
      260      265      270
Pro Asn Val Asp Phe Val Gly Gly Leu His Cys Lys Pro Ala Lys Pro
      275      280      285
Leu Pro Lys Glu Met Glu Glu Phe Val Gln Ser Ser Gly Glu Asn Gly
      290      295      300
Ile Val Val Phe Ser Leu Gly Ser Met Ile Ser Asn Met Ser Glu Glu
      305      310      315
Ser Ala Asn Met Ile Ala Ser Ala Leu Ala Gln Ile Pro Gln Lys Val
      320      325      330
Leu Trp Arg Phe Asp Gly Lys Lys Pro Asn Thr Leu Gly Ser Asn Thr
      335      340      345
Arg Leu Tyr Lys Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro Lys
      350      355      360
Thr Lys Ala Phe Ile Thr His Gly Gly Thr Asn Gly Ile Tyr Glu Ala
      365      370      375
Ile Tyr His Gly Ile Pro Met Val Gly Ile Pro Leu Phe Ala Asp Gln
      380      385      390
His Asp Asn Ile Ala His Met Lys Ala Lys Gly Ala Ala Leu Ser Val
      395      400      405
Asp Ile Arg Thr Met Ser Ser Arg Asp Leu Leu Asn Ala Leu Lys Ser
      410      415      420
Val Ile Asn Asp Pro Val Tyr Lys Glu Asn Val Met Lys Leu Ser Arg
      425      430      435
Ile His His Asp Gln Pro Met Lys Pro Leu Asp Arg Ala Val Phe Trp
      440      445      450
Ile Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu Arg Val Ala
      455      460      465
Ala His Asn Leu Thr Trp Ile Gln Tyr His Ser Leu Asp Val Ile Ala
      470      475      480
Phe Leu Leu Ala Cys Val Ala Thr Val Ile Phe Ile Ile Thr Lys Phe
      485      490      495
Cys Leu Phe Cys Phe Arg Lys Leu Ala Lys Thr Gly Lys Lys Lys
      500      505      510
Arg Asp
      515      520      525
530

```

## SEQUENCE LISTING 1657-2022.txt

<210> 151  
 <211> 265  
 <212> PRT  
 <213> Homo sapiens

<400> 151  
 Met Gly Ser Pro Ser Ala Cys Pro Tyr Arg Val Cys Ile Pro Trp Gln  
 1 5 10 15  
 Gly Leu Leu Thr Ala Ser Leu Thr Phe Trp Asn Leu Pro Asn  
 20 25 30  
 Ser Ala Gln Thr Asn Ile Asp Val Val Pro Phe Asn Val Ala Glu Gly  
 35 40 45  
 Lys Glu Val Leu Leu Val Val His Asn Glu Ser Gln Asn Leu Tyr Gly  
 50 55 60  
 Tyr Asn Trp Tyr Lys Gly Glu Arg Val His Ala Asn Tyr Arg Ile Ile  
 65 70 75 80  
 Gly Tyr Val Lys Asn Ile Ser Gln Glu Asn Ala Pro Gly Pro Ala His  
 85 90 95  
 Asn Gly Arg Glu Thr Ile Tyr Pro Asn Gly Thr Leu Leu Ile Gln Asn  
 100 105 110  
 Val Thr His Asn Asp Ala Gly Phe Tyr Thr Leu His Val Ile Lys Glu  
 115 120 125  
 Asn Leu Val Asn Glu Glu Val Thr Arg Gln Phe Tyr Val Phe Ser Glu  
 130 135 140  
 Pro Pro Lys Pro Ser Ile Thr Ser Asn Asn Phe Asn Pro Val Glu Asn  
 145 150 155 160  
 Lys Asp Ile Val Val Leu Thr Cys Gln Pro Glu Thr Gln Asn Thr Thr  
 165 170 175  
 Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Leu Val Ser Pro Arg Leu  
 180 185 190  
 Leu Leu Ser Thr Asp Asn Arg Thr Leu Val Leu Leu Ser Ala Thr Lys  
 195 200 205  
 Asn Asp Ile Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Gly Ala  
 210 215 220  
 Ser Arg Ser Asp Pro Val Thr Leu Asn Val Arg Tyr Glu Ser Val Gln  
 225 230 235 240  
 Ala Ser Ser Pro Asp Leu Ser Ala Gly Thr Ala Val Ser Ile Met Ile  
 245 250 255  
 Gly Val Leu Ala Gly Met Ala Leu Ile  
 260 265

<210> 152  
 <211> 457  
 <212> PRT  
 <213> Homo sapiens

<400> 152  
 Met Arg Ser Ala Ala Val Leu Ala Leu Leu Leu Cys Ala Gly Gln Val  
 1 5 10 15  
 Thr Ala Leu Pro Val Asn Ser Pro Met Asn Lys Gly Asp Thr Glu Val  
 20 25 30  
 Met Lys Cys Ile Val Glu Val Ile Ser Asp Thr Leu Ser Lys Pro Ser  
 35 40 45  
 Pro Met Pro Val Ser Gln Glu Cys Phe Glu Thr Leu Arg Gly Asp Glu  
 50 55 60  
 Arg Ile Leu Ser Ile Leu Arg His Gln Asn Leu Lys Glu Leu Gln  
 65 70 75 80  
 Asp Leu Ala Leu Gln Gly Ala Lys Glu Arg Ala His Gln Gln Lys Lys  
 85 90 95  
 His Ser Gly Phe Glu Asp Glu Leu Ser Glu Val Leu Glu Asn Gln Ser  
 100 105 110  
 Ser Gln Ala Glu Leu Lys Glu Ala Val Glu Glu Pro Ser Ser Lys Asp  
 115 120 125  
 Val Met Glu Lys Arg Glu Asp Ser Lys Glu Ala Glu Lys Ser Gly Glu  
 130 135 140  
 Ala Thr Asp Gly Ala Arg Pro Gln Ala Leu Pro Glu Pro Met Gln Glu

## SEQUENCE LISTING 1657-2022.txt

```

145      150      155      160
Ser Lys Ala Glu Gly Asn Asn Gln Ala Pro Gly Glu Glu Glu Glu Glu
Glu Glu Glu Ala 165 Asn Thr His Pro 170 Pro Ala Ser Leu Pro Ser Gln
Lys Tyr Pro Gly 180 Pro Gln Ala Glu Gly 185 Asp Ser Glu Gly Leu Ser Gln
Gly Leu Val Asp Arg Glu Lys 200 Gly Leu Ser Ala Glu 205 Pro Gly Trp Gln
Ala Lys Arg Glu Glu Glu Glu Glu Glu Glu Glu Glu Ala Glu Ala Gly
225      230      235      240
Glu Glu Ala Val Pro Glu Glu Glu Gly Pro Thr Val Val Leu Asn Pro
His Pro Ser Leu Gly Tyr Lys Glu Ile Arg Lys Gly Glu Ser Arg Ser
Glu Ala Leu Ala Val Asp Gly Ala Gly Lys Pro Gly Ala Glu Glu Ala
Gln Asp Pro Glu Gly Lys Gly Glu Gln Glu His Ser Gln Gln Lys Glu
305      310      315      320
Lys Ser Gly Glu Leu Glu Gln Glu Glu Glu Arg Leu Ser Lys Glu Trp
Glu Asp Ser Lys Arg Trp Ser Lys Met Asp Gln Leu Ala Lys Glu Leu
Thr Ala Glu Lys Arg Leu Glu Gly Gln Glu Glu Glu Glu Asp Asn Arg
Asp Ser Ser Met Lys Leu Ser Phe Arg Ala Arg Ala Tyr Gly Phe Arg
Gly Pro Gly Pro Gln Leu Arg Arg Gly Trp Arg Pro Ser Ser Arg Glu
385      390      395      400
Asp Ser Leu Glu Ala Gly Leu Pro Leu Gln Val Arg Gly Tyr Pro Glu
Glu Lys Lys Glu Glu Glu Gly Ser Ala Asn Arg Arg Pro Glu Asp Gln
Glu Leu Glu Ser Leu Ser Ala Ile Glu Ala Glu Leu Glu Lys Val Ala
His Gln Leu Gln Ala Leu Arg Arg Gly
450      455

```

```

<210> 153
<211> 266
<212> PRT
<213> Homo sapiens

```

```

<400> 153
Met His Val Asn Gly Lys Val Ala Leu Val Thr Gly Ala Ala Gln Gly
1      5      10      15
Ile Gly Arg Ala Phe Ala Glu Ala Leu Leu Leu Lys Gly Ala Lys Val
20      25      30
Ala Leu Val Asp Trp Asn Leu Glu Ala Gly Val Gln Cys Lys Ala Ala
35      40      45
Leu His Glu Gln Phe Glu Pro Gln Lys Thr Leu Phe Ile Gln Cys Asp
50      55      60
Val Ala Asp Gln Gln Gln Leu Arg Asp Thr Phe Arg Lys Val Val Asp
65      70      75      80
His Phe Gly Arg Leu Asp Ile Leu Val Asn Asn Ala Gly Val Asn Asn
85      90      95
Glu Lys Asn Trp Glu Lys Thr Leu Gln Ile Asn Leu Val Ser Val Ile
100      105      110
Ser Gly Thr Tyr Leu Gly Leu Asp Tyr Met Ser Lys Gln Asn Gly Gly
115      120      125
Glu Gly Gly Ile Ile Ile Asn Met Ser Ser Leu Ala Gly Leu Met Pro
130      135      140
Val Ala Gln Gln Pro Val Tyr Cys Ala Ser Lys His Gly Ile Val Gly
145      150      155      160

```



## SEQUENCE LISTING 1657-2022.txt

Phe Thr Arg Ser Ala Ala Leu Ala Ala Asn Leu Met Asn Ser Gly Val  
 165 170 175  
 Arg Leu Asn Ala Ile Cys Pro Gly Phe Val Asn Thr Ala Ile Leu Glu  
 180 185 190  
 Ser Ile Glu Lys Glu Glu Asn Met Gly Gln Tyr Ile Glu Tyr Lys Asp  
 195 200 205  
 His Ile Lys Asp Met Ile Lys Tyr Tyr Gly Ile Leu Asp Pro Pro Leu  
 210 215 220  
 Ile Ala Asn Gly Leu Ile Thr Leu Ile Glu Asp Asp Ala Leu Asn Gly  
 225 230 235 240  
 Ala Ile Met Lys Ile Thr Thr Ser Lys Gly Ile His Phe Gln Asp Tyr  
 245 250 255  
 Asp Thr Thr Pro Phe Gln Ala Lys Thr Gln  
 260 265

<210> 154  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<400> 154  
 Met Phe Ser Ala Ile Arg Ser Gln His Ser Gly Val Asp Ile Cys Ile  
 1 5 10 15  
 Asn Asn Ala Gly Leu Ala Arg Pro Asp Thr Leu Leu Ser Gly Ser Thr  
 20 25 30  
 Ser Gly Trp Lys Asp Met Phe Asn Val Asn Val Leu Ala Leu Ser Ile  
 35 40 45  
 Cys Thr Arg Glu Ala Tyr Gln Ser Met Lys Glu Arg Asn Val Asp Asp  
 50 55 60  
 Gly His Ile Ile Asn Ile Asn Ser Met Ser Gly His Arg Val Leu Pro  
 65 70 75 80  
 Leu Ser Val Thr His Phe Tyr Ser Ala Thr Lys Tyr Ala Val Thr Ala  
 85 90 95  
 Leu Thr Glu Gly Leu Arg Gln Glu Leu Arg Glu Ala Gln Thr His Ile  
 100 105 110  
 Arg Ala Thr Cys Ile Ser Pro Gly Val Val Glu Thr Gln Phe Ala Phe  
 115 120 125  
 Lys Leu His Asp Lys Asp Pro Glu Lys Ala Ala Ala Thr Tyr Glu Gln  
 130 135 140  
 Met Lys Cys Leu Lys Pro Glu Asp Val Ala Glu Ala Val Ile Tyr Val  
 145 150 155 160  
 Leu Ser Thr Pro Ala His Ile Gln Ile Gly Asp Ile Gln Met Arg Pro  
 165 170 175  
 Thr Glu Gln Val Thr  
 180

<210> 155  
 <211> 312  
 <212> PRT  
 <213> Homo sapiens

<400> 155  
 Met Arg Met Leu Leu Ala Leu Leu Ala Leu Ser Ala Ala Arg Pro Ser  
 1 5 10 15  
 Ala Ser Ala Glu Ser His Trp Cys Tyr Glu Val Gln Ala Glu Ser Ser  
 20 25 30  
 Asn Tyr Pro Cys Leu Val Pro Val Lys Trp Gly Gly Asn Cys Gln Lys  
 35 40 45  
 Asp Arg Gln Ser Pro Ile Asn Ile Val Thr Thr Lys Ala Lys Val Asp  
 50 55 60  
 Lys Lys Leu Gly Arg Phe Phe Phe Ser Gly Tyr Asp Lys Lys Gln Thr  
 65 70 75 80  
 Trp Thr Val Gln Asn Asn Gly His Ser Val Met Met Leu Leu Glu Asn  
 85 90 95  
 Lys Ala Ser Ile Ser Gly Gly Gly Leu Pro Ala Pro Tyr Gln Ala Lys

## SEQUENCE LISTING 1657-2022.txt

100 105 110  
 Gln Leu His Leu His Trp Ser Asp Leu Pro Tyr Lys Gly Ser Glu His  
 115 120 125  
 Ser Leu Asp Gly Glu His Phe Ala Met Glu Met His Ile Val His Glu  
 130 135 140  
 Lys Glu Lys Gly Thr Ser Arg Asn Val Lys Glu Ala Gln Asp Pro Glu  
 145 150 155 160  
 Asp Glu Ile Ala Val Leu Ala Phe Leu Val Glu Ala Gly Thr Gln Val  
 165 170 175  
 Asn Glu Gly Phe Gln Pro Leu Val Glu Ala Leu Ser Asn Ile Pro Lys  
 180 185 190  
 Pro Glu Met Ser Thr Thr Met Ala Glu Ser Ser Leu Leu Asp Leu Leu  
 195 200 205  
 Pro Lys Glu Glu Lys Leu Arg His Tyr Phe Arg Tyr Leu Gly Ser Leu  
 210 215 220  
 Thr Thr Pro Thr Cys Asp Glu Lys Val Val Trp Thr Val Phe Arg Glu  
 225 230 235 240  
 Pro Ile Gln Leu His Arg Glu Gln Ile Leu Ala Phe Ser Gln Lys Leu  
 245 250 255  
 Tyr Tyr Asp Lys Glu Gln Thr Val Ser Met Lys Asp Asn Val Arg Pro  
 260 265 270  
 Leu Gln Gln Leu Gly Gln Arg Thr Val Ile Lys Ser Gly Ala Pro Gly  
 275 280 285  
 Arg Pro Leu Pro Trp Ala Leu Pro Ala Leu Leu Gly Pro Met Leu Ala  
 290 295 300  
 Cys Leu Leu Ala Gly Phe Leu Arg  
 305 310

<210> 156  
 <211> 398  
 <212> PRT  
 <213> Homo sapiens

<400> 156  
 Met Leu Arg Leu Tyr Val Leu Val Met Gly Val Ser Ala Phe Thr Leu  
 1 5 10 15  
 Gln Pro Ala Ala His Thr Gly Ala Ala Arg Ser Cys Arg Phe Arg Gly  
 20 25 30  
 Arg His Tyr Lys Arg Glu Phe Arg Leu Glu Gly Glu Pro Val Ala Leu  
 35 40 45  
 Arg Cys Pro Gln Val Pro Tyr Trp Leu Trp Ala Ser Val Ser Pro Arg  
 50 55 60  
 Ile Asn Leu Thr Trp His Lys Asn Asp Ser Ala Arg Thr Val Pro Gly  
 65 70 75 80  
 Glu Glu Glu Thr Arg Met Trp Ala Gln Asp Gly Ala Leu Trp Leu Leu  
 85 90 95  
 Pro Ala Leu Gln Glu Asp Ser Gly Thr Tyr Val Cys Thr Thr Arg Asn  
 100 105 110  
 Ala Ser Tyr Cys Asp Lys Met Ser Ile Glu Leu Arg Val Phe Glu Asn  
 115 120 125  
 Thr Asp Ala Phe Leu Pro Phe Ile Ser Tyr Pro Gln Ile Leu Thr Leu  
 130 135 140  
 Ser Thr Ser Gly Val Leu Val Cys Pro Asp Leu Ser Glu Phe Thr Arg  
 145 150 155 160  
 Asp Lys Thr Asp Val Lys Ile Gln Trp Tyr Lys Asp Ser Leu Leu Leu  
 165 170 175  
 Asp Lys Asp Asn Glu Lys Phe Leu Ser Val Arg Gly Thr Thr His Leu  
 180 185 190  
 Leu Val His Asp Val Ala Leu Glu Asp Ala Gly Tyr Tyr Arg Cys Val  
 195 200 205  
 Leu Thr Phe Ala His Glu Gly Gln Gln Tyr Asn Ile Thr Arg Ser Ile  
 210 215 220  
 Glu Leu Arg Ile Lys Lys Lys Glu Glu Thr Ile Pro Val Ile Ile  
 225 230 235 240  
 Ser Pro Leu Lys Thr Ile Ser Ala Ser Leu Gly Ser Arg Leu Thr Ile  
 245 250 255

## SEQUENCE LISTING 1657-2022.txt

```

Pro Cys Lys Val Phe Leu Gly Thr Gly Thr Pro Leu Thr Thr Met Leu
      260      265      270
Trp Trp Thr Ala Asn Asp Thr His Ile Glu Ser Ala Tyr Pro Gly Gly
      275      280      285
Arg Val Thr Glu Gly Pro Arg Gln Glu Tyr Ser Glu Asn Asn Glu Asn
      290      295      300
Tyr Ile Glu Val Pro Leu Ile Phe Asp Pro Val Thr Arg Glu Asp Leu
      305      310      315
His Met Asp Phe Lys Cys Val Val His Asn Thr Leu Ser Phe Gln Thr
      325      330      335
Leu Arg Thr Thr Val Lys Glu Ala Ser Ser Thr Phe Ser Trp Gly Ile
      340      345      350
Val Leu Ala Pro Leu Ser Leu Ala Phe Leu Val Leu Gly Gly Ile Trp
      355      360      365
Met His Arg Arg Cys Lys His Arg Thr Gly Lys Ala Asp Gly Leu Thr
      370      375      380
Val Leu Trp Pro His His Gln Asp Phe Gln Ser Tyr Pro Lys
      385      390      395

```

<210> 157  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

```

<400> 157
Met Glu Lys Phe Asn Thr Ile Ser Ala Ser Lys Cys Asn Lys Glu Thr
  1      5      10      15
Val Ala Met Lys Glu Lys Cys Lys Phe Gly Met Thr Ser Thr Ile Pro
      20      25      30
Ser Gly His Val Trp Arg Asn Thr Trp Asn Pro Val Ser Cys Ser Leu
      35      40      45
Ala Thr Val Lys Met Lys Glu Cys Leu Arg Gly Lys Leu Ile Tyr Leu
      50      55      60
Met Gly Asp Ser Thr Ile Arg Gln Trp Met Glu Tyr Phe Lys Ala Ser
      65      70      75      80
Ile Asn Thr Leu Lys Ser Val Asp Leu His Glu Ser Gly Lys Leu Gln
      85      90      95
His Gln Leu Ala Val Asp Leu Asp Arg Asn Ile Asn Ile Gln Trp Gln
      100      105      110
Lys Tyr Cys Tyr Pro Leu Ile Gly Ser Met Thr Tyr Ser Val Lys Glu
      115      120      125
Met Glu Tyr Leu Thr Arg Ala Ile Asp Arg Thr Gly Gly Glu Lys Lys
      130      135      140
Tyr Cys His Cys Tyr Phe Pro Gly Pro Ala Phe Gln Thr Leu Ser His
      145      150      155      160

```

<210> 158  
 <211> 267  
 <212> PRT  
 <213> Homo sapiens

```

<400> 158
Met Met Ser Ser Lys Pro Thr Ser His Ala Glu Val Asn Glu Thr Ile
  1      5      10      15
Pro Asn Pro Tyr Pro Pro Gly Ser Phe Met Ala Pro Gly Phe Gln Gln
      20      25      30
Pro Leu Gly Ser Ile Asn Leu Glu Asn Gln Ala Gln Gly Ala Gln Arg
      35      40      45
Ala Gln Pro Tyr Gly Ile Thr Ser Pro Gly Ile Phe Ala Ser Ser Gln
      50      55      60
Pro Gly Gln Gly Asn Ile Gln Met Ile Asn Pro Ser Val Gly Thr Ala
      65      70      75      80
Val Met Asn Phe Lys Glu Glu Ala Lys Ala Leu Gly Val Ile Gln Ile
      85      90      95
Met Val Gly Leu Met His Ile Gly Phe Gly Ile Val Leu Cys Leu Ile

```

## SEQUENCE LISTING 1657-2022.txt

```

100      105      110
Ser Phe Ser Phe Arg Glu Val Leu Gly Phe Ala Ser Thr Ala Val Ile
115
Gly Gly Tyr Pro Phe Trp Gly Gly Leu Ser Phe Ile Ile Ser Gly Ser
130
Leu Ser Val Ser Ala Ser Lys Glu Leu Ser Arg Cys Leu Val Lys Gly
145
Ser Leu Gly Met Asn Ile Val Ser Ser Ile Leu Ala Phe Ile Gly Val
165
Ile Leu Leu Leu Val Asp Met Cys Ile Asn Gly Val Ala Gly Gln Asp
180
Tyr Trp Ala Val Leu Ser Gly Lys Gly Ile Ser Ala Thr Leu Met Ile
195
Phe Ser Leu Leu Glu Phe Phe Val Ala Cys Ala Thr Ala His Phe Ala
210
Asn Gln Ala Asn Thr Thr Thr Asn Met Ser Val Leu Val Ile Pro Asn
225
Met Tyr Glu Ser Asn Pro Val Thr Pro Ala Ser Ser Ser Ala Pro Pro
245
Arg Cys Asn Asn Tyr Ser Ala Asn Ala Pro Lys
260

```

<210> 159  
 <211> 157  
 <212> PRT  
 <213> Homo sapiens

```

<400> 159
Met Leu Val Leu Leu Ala Gly Ile Phe Val Val His Ile Ala Thr Val
1      5      10
Ile Met Leu Phe Val Ser Thr Ile Ala Asn Val Trp Leu Val Ser Asn
20
Thr Val Asp Ala Ser Val Gly Leu Trp Lys Asn Cys Thr Asn Ile Ser
35
Cys Ser Asp Ser Leu Ser Tyr Ala Ser Glu Asp Ala Leu Lys Thr Val
50
Gln Ala Phe Met Ile Leu Ser Ile Ile Phe Cys Val Ile Ala Leu Leu
65
Val Phe Val Phe Gln Leu Phe Thr Met Glu Lys Gly Asn Arg Phe Phe
85
Leu Ser Gly Ala Thr Thr Leu Val Cys Trp Leu Cys Ile Leu Val Gly
100
Val Ser Ile Tyr Thr Ser His Tyr Ala Asn Arg Asp Gly Thr Gln Tyr
115
His His Gly Tyr Ser Tyr Ile Leu Gly Trp Ile Cys Phe Cys Phe Ser
130
Phe Ile Ile Gly Val Leu Tyr Leu Val Leu Arg Lys Lys
145
150
155

```

<210> 160  
 <211> 1035  
 <212> PRT  
 <213> Homo sapiens

```

<400> 160
Met Ser Thr Glu Asn Val Glu Gly Lys Pro Ser Asn Leu Gly Glu Arg
1      5      10
Gly Arg Ala Arg Ser Ser Thr Phe Leu Arg Val Val Gln Pro Met Phe
20
Asn His Ser Ile Phe Thr Ser Ala Val Ser Pro Ala Ala Glu Arg Ile
35
Arg Phe Ile Leu Gly Glu Glu Asp Asp Ser Pro Ala Pro Pro Gln Leu
50
Phe Thr Glu Leu Asp Glu Leu Leu Ala Val Asp Gly Gln Glu Met Glu
65
70
75
80

```

## SEQUENCE LISTING 1657-2022.txt

Trp Lys Glu Thr Ala Arg Trp Ile Lys Phe Glu Glu Lys Val Glu Gln  
 85 90 95  
 Gly Gly Glu Arg Trp Ser Lys Pro His Val Ala Thr Leu Ser Leu His  
 100 105 110  
 Ser Leu Phe Glu Leu Arg Thr Cys Met Glu Lys Gly Ser Ile Met Leu  
 115 120 125  
 Asp Arg Glu Ala Ser Ser Leu Pro Gln Leu Val Glu Met Ile Val Asp  
 130 135 140  
 His Gln Ile Glu Thr Gly Leu Leu Lys Pro Glu Leu Lys Asp Lys Val  
 145 150 155 160  
 Thr Tyr Thr Leu Leu Arg Lys His Arg His Gln Thr Lys Lys Ser Asn  
 165 170 175  
 Leu Arg Ser Leu Ala Asp Ile Gly Lys Thr Val Ser Ser Ala Ser Arg  
 180 185 190  
 Met Phe Thr Asn Pro Asp Asn Gly Ser Pro Ala Met Thr His Arg Asn  
 195 200 205  
 Leu Thr Ser Ser Ser Leu Asn Asp Ile Ser Asp Lys Pro Glu Lys Asp  
 210 215 220  
 Gln Leu Lys Asn Lys Phe Met Lys Lys Leu Pro Arg Asp Ala Glu Ala  
 225 230 235 240  
 Ser Asn Val Leu Val Gly Glu Val Asp Phe Leu Asp Thr Pro Phe Ile  
 245 250 255  
 Ala Phe Val Arg Leu Gln Gln Ala Val Met Leu Gly Ala Leu Thr Glu  
 260 265 270  
 Val Pro Val Pro Thr Arg Phe Leu Phe Ile Leu Leu Gly Pro Lys Gly  
 275 280 285  
 Lys Ala Lys Ser Tyr His Glu Ile Gly Arg Ala Ile Ala Thr Leu Met  
 290 295 300  
 Ser Asp Glu Val Phe His Asp Ile Ala Tyr Lys Ala Lys Asp Arg His  
 305 310 315 320  
 Asp Leu Ile Ala Gly Ile Asp Glu Phe Leu Asp Glu Val Ile Val Leu  
 325 330 335  
 Pro Pro Gly Glu Trp Asp Pro Ala Ile Arg Ile Glu Pro Pro Lys Ser  
 340 345 350  
 Leu Pro Ser Ser Asp Lys Arg Lys Asn Met Tyr Ser Gly Gly Glu Asn  
 355 360 365  
 Val Gln Met Asn Gly Asp Thr Pro His Asp Gly Gly His Gly Gly Gly  
 370 375 380  
 Gly His Gly Asp Cys Glu Glu Leu Gln Arg Thr Gly Arg Phe Cys Gly  
 385 390 395 400  
 Gly Leu Ile Lys Asp Ile Lys Arg Lys Ala Pro Phe Phe Ala Ser Asp  
 405 410 415  
 Phe Tyr Asp Ala Leu Asn Ile Gln Ala Leu Ser Ala Ile Leu Phe Ile  
 420 425 430  
 Tyr Leu Ala Thr Val Thr Asn Ala Ile Thr Phe Gly Gly Leu Leu Gly  
 435 440 445  
 Asp Ala Thr Asp Asn Met Gln Gly Val Leu Glu Ser Phe Leu Gly Thr  
 450 455 460  
 Ala Val Ser Gly Ala Ile Phe Cys Leu Phe Ala Gly Gln Pro Leu Thr  
 465 470 475 480  
 Ile Leu Ser Ser Thr Gly Pro Val Leu Val Phe Glu Arg Leu Leu Phe  
 485 490 495  
 Asn Phe Ser Lys Asp Asn Asn Phe Asp Tyr Leu Glu Phe Arg Leu Trp  
 500 505 510  
 Ile Gly Leu Trp Ser Ala Phe Leu Cys Leu Ile Leu Val Ala Thr Asp  
 515 520 525  
 Ala Ser Phe Leu Val Gln Tyr Phe Thr Arg Phe Thr Glu Glu Gly Phe  
 530 535 540  
 Ser Ser Leu Ile Ser Phe Ile Phe Ile Tyr Asp Ala Phe Lys Lys Met  
 545 550 555 560  
 Ile Lys Leu Ala Asp Tyr Tyr Pro Ile Asn Ser Asn Phe Lys Val Gly  
 565 570 575  
 Tyr Asn Thr Leu Phe Ser Cys Thr Cys Val Pro Pro Asp Pro Ala Asn  
 580 585 590  
 Ile Ser Ile Ser Asn Asp Thr Thr Leu Ala Pro Glu Tyr Leu Pro Thr  
 595 600 605  
 Met Ser Ser Thr Asp Met Tyr His Asn Thr Thr Phe Asp Trp Ala Phe

## SEQUENCE LISTING 1657-2022.txt

610  
 Leu Ser Lys Lys Glu Cys 615 Ser Lys Tyr Gly Gly 620 Asn Leu Val Gly Asn  
 625 Asn Cys Asn Phe Val 630 Pro Asp Ile Thr Leu 635 Met Ser Phe Ile Leu 640 Phe  
 Leu Gly Thr Tyr 645 Ser Ser Met Ala 650 Leu Lys Lys Phe Lys 655 Thr Ser  
 Pro Tyr Phe 660 Pro Thr Thr Ala Arg 665 Lys Leu Ile Ser Asp 670 Phe Ala Ile  
 Ile Leu Ser Ile Leu Ile Phe 680 Cys Val Ile Asp Ala 685 Leu Val Gly Val  
 690 Asp Thr Pro Lys Leu Ile 695 Val Pro Ser Glu Phe 700 Lys Pro Thr Ser Pro  
 705 Asn Arg Gly Trp Phe 710 Val Pro Pro Phe Gly 715 Glu Asn Pro Trp Trp Val  
 Cys Leu Ala Ala 725 Ile Pro Ala Leu 730 Leu Val Thr Ile Leu 735 Ile Phe  
 Met Asp Gln Gln Ile Thr Ala Val 745 Ile Val Asn Arg Lys Glu His Lys  
 755 Leu Lys Lys Gly Ala Gly Tyr 760 His Leu Asp Leu Phe Trp Val Ala Ile  
 770 Leu Met Val Ile Cys Ser Leu Met Ala Leu Pro Trp Tyr Val Ala Ala  
 785 Thr Val Ile Ser Ile 805 Ala His Ile Asp Ser 810 Leu Lys Met Glu Thr Glu  
 Thr Ser Ala Pro Gly Glu Gln Pro Lys Phe Leu Gly Val Arg Glu Gln  
 Arg Val Thr 820 Gly Thr Leu Val Phe 825 Ile Leu Thr Gly Leu Ser Val Phe  
 Met Ala Pro Ile Leu Lys Phe 840 Ile Pro Met Pro Val Leu Tyr Gly Val  
 850 Phe Leu Tyr Met Gly Val 855 Ala Ser Leu Asn Gly Val Gln Phe Met Asp  
 865 Arg Leu Lys Leu Leu 870 Leu Met Pro Leu Lys His Gln Pro Asp Phe Ile  
 Tyr Leu Arg His 885 Val Pro Leu Arg Arg Val His Leu Phe Thr Phe Leu  
 Gln Val Leu Cys Leu Ala Leu Leu Trp Ile Leu Lys Ser Thr Val Ala  
 915 Ala Ile Phe Pro Val Met 920 Ile Leu Ala Leu Val Ala Val Arg Lys  
 930 Gly Met Asp Tyr Leu Phe Ser Gln His Asp Leu Ser Phe Leu Asp Asp  
 945 Val Ile Pro Glu Lys 950 Asp Lys Lys Lys Lys Glu Asp Glu Lys Lys Lys  
 Lys Lys Lys Lys Gly Ser Leu Asp Ser Asp Asn Asp Asp Ser Asp Cys  
 980 Pro Tyr Ser Glu Lys Val Pro Ser Ile Lys Ile Pro Met Asp Ile Met  
 995 Glu Gln Gln Pro Phe Leu Ser Asp Ser Lys Pro Ser Asp Arg Glu Arg  
 1010 Ser Pro Thr Phe Leu Glu Arg His Thr Ser Cys 1020  
 1025 1030 1035

<210> 161  
 <211> 375  
 <212> PRT  
 <213> Homo sapiens

<400> 161  
 Met Ser Thr Ala Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp  
 1 5 10 15  
 Glu Leu Lys Lys Pro Phe Ser Ile Glu Val Glu Val Ala Pro Pro  
 20 25 30  
 Lys Ala His Glu Val Arg Ile Lys Met Val Ala Ala Gly Ile Cys Arg  
 35 40 45

## SEQUENCE LISTING 1657-2022.txt

```

Ser Asp Glu His Val Val Ser Gly Asn Leu Val Thr Pro Leu Pro Val
50 55 60
Ile Leu Gly His Glu Ala Ala Gly Ile Val Glu Ser Val Gly Glu Gly
65 70 75 80
Val Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Thr Pro
85 90 95
Gln Cys Gly Lys Cys Arg Ile Cys Lys Asn Pro Glu Ser Asn Tyr Cys
100 105 110
Leu Lys Asn Asp Leu Gly Asn Pro Arg Gly Thr Leu Gln Asp Gly Thr
115 120 125
Arg Arg Phe Thr Cys Ser Gly Lys Pro Ile His His Phe Val Gly Val
130 135 140
Ser Thr Phe Ser Gln Tyr Thr Val Val Asp Glu Asn Ala Val Ala Lys
145 150 155 160
Ile Asp Ala Ala Ser Pro Leu Glu Lys Val Cys Leu Ile Gly Cys Gly
165 170 175
Phe Ser Thr Gly Tyr Gly Ser Ala Val Lys Val Ala Lys Val Thr Pro
180 185 190
Gly Ser Thr Cys Ala Val Phe Gly Leu Gly Gly Val Gly Leu Ser Val
195 200 205
Val Met Gly Cys Lys Ala Ala Gly Ala Ala Arg Ile Ile Ala Val Asp
210 215 220
Ile Asn Lys Asp Lys Phe Ala Lys Ala Lys Glu Leu Gly Ala Thr Glu
225 230 235 240
Cys Ile Asn Pro Gln Asp Tyr Lys Lys Pro Ile Gln Glu Val Leu Lys
245 250 255
Glu Met Thr Asp Gly Gly Val Asp Phe Ser Phe Glu Val Ile Gly Arg
260 265 270
Leu Asp Thr Met Met Ala Ser Leu Leu Cys Cys His Glu Ala Cys Gly
275 280 285
Thr Ser Val Ile Val Gly Val Pro Pro Asp Ser Gln Asn Leu Ser Ile
290 295 300
Asn Pro Met Leu Leu Leu Thr Gly Arg Thr Trp Lys Gly Ala Ile Phe
305 310 315 320
Gly Gly Phe Lys Ser Lys Glu Ser Val Pro Lys Leu Val Ala Asp Phe
325 330 335
Met Ala Lys Lys Phe Ser Leu Asp Ala Leu Ile Thr Asn Ile Leu Pro
340 345 350
Phe Glu Lys Ile Asn Glu Gly Phe Asp Leu Leu Arg Ser Gly Lys Ser
355 360 365
Ile Arg Thr Val Leu Thr Phe
370 375

```

<210> 162  
 <211> 526  
 <212> PRT  
 <213> Homo sapiens

```

<400> 162
Met Gly His Leu Ser Ala Pro Leu His Arg Val Arg Val Pro Trp Gln
1 5 10 15
Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
20 25 30
Thr Ala Gln Leu Thr Thr Glu Ser Met Pro Phe Asn Val Ala Glu Gly
35 40 45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Gln Leu Phe Gly
50 55 60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Val
65 70 75 80
Gly Tyr Ala Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Asn Ser
85 90 95
Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val
100 105 110
Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp
115 120 125
Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu

```

## SEQUENCE LISTING 1657-2022.txt

```

130          135          140
Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys
145 Asp Ala Val Ala Phe 150 Cys Glu Pro Glu 155 Gln Asp Thr Thr 160
Leu Trp Trp Ile 165 Asn Asn Gln Ser Leu 170 Pro Val Ser Pro Arg Leu Gln
Leu Ser Asn 180 Gly Asn Arg Thr Leu 185 Leu Leu Ser Val Thr Arg Asn
Asp Thr Gly Pro Tyr Glu Cys 200 Glu Ile Gln Asn Pro Val Ser Ala Asn
210 Arg Ser Asp Pro Val Thr 215 Leu Asn Val Thr Tyr 220 Gly Pro Asp Thr Pro
225 Thr Ile Ser Pro Ser Asp Thr Tyr Tyr Arg Pro Gly Ala Asn Leu Ser
Leu Ser Cys Tyr 245 Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Leu
Ile Asn Gly Thr Phe Gln Gln Ser 265 Thr Gln Glu Leu Phe Ile Pro Asn
Ile Thr Val Asn Asn Ser Gly 280 Ser Tyr Thr Cys His Ala Asn Asn Ser
Val Thr Gly Cys Asn Arg Thr Thr Val Lys Thr Ile Ile Val Thr Glu
305 Leu Ser Pro Val Val 310 Lys Pro Gln Ile Lys Ala Ser Lys Thr Thr
Val Thr Gly Asp Lys Asp Ser Val Asn Leu Thr Cys Ser Thr Asn Asp
Thr Gly Ile Ser Ile Arg Trp Phe 345 Phe Lys Asn Gln Ser Leu Pro Ser
Ser Glu Arg Met Lys Leu Ser 375 Gln Gly Asn Thr Thr Leu Ser Ile Asn
Pro Val Lys Arg Glu Asp 390 Ala Gly Thr Tyr Trp Cys Glu Val Phe Asn
385 Pro Ile Ser Lys Asn Gln Ser Asp Pro Ile Met Leu Asn Val Asn Tyr
Asn Ala Leu Pro Gln Glu Asn Gly Leu 425 Ser Pro Gly Ala Ile Ala Gly
Ile Val Ile Gly Val Val Ala Leu Val Ala Leu Ile Ala Val Ala Leu
Ala Cys Phe Leu His Phe Gly 440 Lys Thr Gly Arg Ala Ser Asp Gln Arg
Asp Leu Thr Glu His Lys 455 Pro Ser Val Ser Asn His Thr Gln Asp His
465 Ser Asn Asp Pro Pro 470 Asn Lys Met Asn Glu Val Thr Tyr Ser Thr Leu
Asn Phe Glu Ala Gln Gln Pro Thr Gln 490 Pro Thr Ser Ala Ser Pro Ser
Leu Thr Ala Thr Glu Ile Ile Tyr 505 Ser Glu Val Lys Lys 510 Gln
515          520          525

```

<210> 163  
 <211> 255  
 <212> PRT  
 <213> Homo sapiens

```

<400> 163
Met His Gln Lys Ile Ala Arg Glu Met Asn Leu Ser Glu Thr Ala Phe
1 5 10 15
Ile Arg Lys Leu His Pro Thr Asp Asn Phe Ala Gln Ser Ser Cys Phe
20 25 30
Gly Leu Arg Trp Phe Thr Pro Ala Ser Glu Val Pro Leu Cys Gly His
35 40 45
Ala Thr Leu Ala Ser Ala Ala Val Leu Phe His Lys Ile Lys Asn Met
50 55 60
Asn Ser Thr Leu Thr Phe Val Thr Leu Ser Gly Glu Leu Arg Ala Arg
65 70 75 80

```



## SEQUENCE LISTING 1657-2022.txt

```

Arg Ala Glu Asp Gly Ile Val Leu Asp Leu Pro Leu Tyr Pro Ala His
      85      90      95
Pro Gln Asp Phe His Glu Val Glu Asp Leu Ile Lys Thr Ala Ile Gly
      100      105      110
Asn Thr Leu Val Gln Asp Ile Cys Tyr Ser Pro Asp Thr Gln Lys Leu
      115      120      125
Leu Val Arg Leu Ser Asp Val Tyr Asn Arg Ser Phe Leu Glu Asn Leu
      130      135      140
Lys Val Asn Thr Glu Asn Leu Leu Gln Val Glu Asn Thr Gly Lys Val
      145      150      155      160
Lys Gly Leu Ile Leu Thr Leu Lys Gly Glu Pro Gly Gly Gln Thr Gln
      165      170      175
Ala Phe Asp Phe Tyr Ser Arg Tyr Phe Ala Pro Trp Val Gly Val Ala
      180      185      190
Glu Asp Pro Val Thr Gly Ser Ala His Ala Val Leu Ser Ser Tyr Trp
      195      200      205
Ser Gln His Leu Gly Lys Lys Glu Met His Ala Phe Gln Cys Ser His
      210      215      220
Arg Gly Gly Glu Leu Gly Ile Ser Leu Arg Pro Asp Gly Arg Val Asp
      225      230      235      240
Ile Arg Gly Gly Ala Val Val Leu Glu Gly Thr Leu Thr Ala
      245      250      255

```

```

<210> 164
<211> 622
<212> PRT
<213> Homo sapiens

```

```

<400> 164
Met Pro Pro Gln Leu Gln Asn Gly Leu Asn Leu Ser Ala Lys Val Val
  1      5      10      15
Gln Gly Ser Leu Asp Ser Leu Pro Gln Ala Val Arg Glu Phe Leu Glu
      20      25      30
Asn Asn Ala Glu Leu Cys Gln Pro Asp His Ile His Ile Cys Asp Gly
      35      40      45
Ser Glu Glu Glu Asn Gly Arg Leu Leu Gly Gln Met Glu Glu Glu Gly
      50      55      60
Ile Leu Arg Arg Leu Lys Lys Tyr Asp Asn Cys Trp Leu Ala Leu Thr
      65      70      75      80
Asp Pro Arg Asp Val Ala Arg Ile Glu Ser Lys Thr Val Ile Val Thr
      85      90      95
Gln Glu Gln Arg Asp Thr Val Pro Ile Pro Lys Thr Gly Leu Ser Gln
      100      105      110
Leu Gly Arg Trp Met Ser Glu Glu Asp Phe Glu Lys Ala Phe Asn Ala
      115      120      125
Arg Phe Pro Gly Cys Met Lys Gly Arg Thr Met Tyr Val Ile Pro Phe
      130      135      140
Ser Met Gly Pro Leu Gly Ser Pro Leu Ser Lys Ile Gly Ile Glu Leu
      145      150      155      160
Thr Asp Ser Pro Tyr Val Val Ala Ser Met Arg Ile Met Thr Arg Met
      165      170      175
Gly Thr Pro Val Leu Glu Ala Leu Gly Asp Gly Glu Phe Val Lys Cys
      180      185      190
Leu His Ser Val Gly Cys Pro Leu Pro Leu Gln Lys Pro Leu Val Asn
      195      200      205
Asn Trp Pro Cys Asn Pro Glu Leu Thr Leu Ile Ala His Leu Pro Asp
      210      215      220
Arg Arg Glu Ile Ile Ser Phe Gly Ser Gly Tyr Gly Gly Asn Ser Leu
      225      230      235      240
Leu Gly Lys Lys Cys Phe Ala Leu Arg Met Ala Ser Arg Leu Ala Glu
      245      250      255
Glu Glu Gly Trp Leu Ala Glu His Met Leu Ile Leu Gly Ile Thr Asn
      260      265      270
Pro Glu Gly Glu Lys Lys Tyr Leu Ala Ala Ala Phe Pro Ser Ala Cys
      275      280      285
Gly Lys Thr Asn Leu Ala Met Met Asn Pro Ser Leu Pro Gly Trp Lys

```

## SEQUENCE LISTING 1657-2022.txt

```

290          295          300
val Glu Cys val Gly Asp Asp Ile Ala Trp Met Lys Phe Asp Ala Gln
305          310          315          320
Gly His Leu Arg Ala Ile Asn Pro Glu Asn Gly Phe Phe Gly val Ala
          325          330          335
Pro Gly Thr Ser val Lys Thr Asn Pro Asn Ala Ile Lys Thr Ile Gln
          340          345          350
Lys Asn Thr Ile Phe Thr Asn val Ala Glu Thr Ser Asp Gly Gly val
          355          360          365
Tyr Trp Glu Gly Ile Asp Glu Pro Leu Ala Ser Gly val Thr Ile Thr
          370          375          380
Ser Trp Lys Asn Lys Glu Trp Ser Ser Glu Asp Gly Glu Pro Cys Ala
          385          390          395          400
His Pro Asn Ser Arg Phe Cys Thr Pro Ala Ser Gln Cys Pro Ile Ile
          405          410          415
Asp Ala Ala Trp Glu Ser Pro Glu Gly val Pro Ile Glu Gly Ile Ile
          420          425          430
Phe Gly Gly Arg Arg Pro Ala Gly val Pro Leu val Tyr Glu Ala Leu
          435          440          445
Ser Trp Gln His Gly val Phe val Gly Ala Ala Met Arg Ser Glu Ala
          450          455          460
Thr Ala Ala Ala Glu His Lys Gly Lys Ile Ile Met His Asp Pro Phe
          465          470          475          480
Ala Met Arg Pro Phe Gly Tyr Asn Phe Gly Lys Tyr Leu Ala His
          485          490          495
Trp Leu Ser Met Ala Gln His Pro Ala Ala Lys Leu Pro Lys Ile Phe
          500          505          510
His val Asn Trp Phe Arg Lys Asp Lys Glu Gly Lys Phe Leu Trp Pro
          515          520          525
Gly Phe Gly Glu Asn Ser Arg val Leu Glu Trp Met Phe Asn Arg Ile
          530          535          540
Asp Gly Lys Ala Ser Thr Asn val Thr Pro Ile Gly Tyr Ile Pro Lys
          545          550          555          560
Glu Asp Ala Leu Asn Leu Lys Gly Leu Gly His Ile Asn Met Met Glu
          565          570          575
Leu Phe Ser Ile Ser Lys Glu Phe Trp Asp Lys Glu val Glu Asp Ile
          580          585          590
Glu Lys Tyr Leu val Asp Gln val Asn Ala Asp Leu Pro Cys Glu Ile
          595          600          605
Glu Arg Glu Ile Leu Ala Leu Lys Gln Arg Ile Ser Gln Met
          610          615          620

```

<210> 165  
 <211> 530  
 <212> PRT  
 <213> Homo sapiens

```

<400> 165
Met Ser Leu Lys Trp Met Ser val Phe Leu Leu Met Gln Leu Ser Cys
1          5          10          15
Tyr Phe Ser Ser Gly Ser Cys Gly Lys val Leu val Trp Pro Thr Glu
          20          25          30
Tyr Ser His Trp Ile Asn Met Lys Thr Ile Leu Glu Glu Leu val Gln
          35          40          45
Arg Gly His Glu val Ile val Leu Thr Ser Ser Ala Ser Ile Leu val
          50          55          60
Asn Ala Ser Lys Ser Ser Ala Ile Lys Leu Glu val Tyr Pro Thr Ser
          65          70          75          80
Leu Thr Lys Asn Asp Leu Glu Asp Phe Phe Met Lys Met Phe Asp Arg
          85          90          95
Trp Thr Tyr Ser Ile Ser Lys Asn Thr Phe Trp Ser Tyr Phe Ser Gln
          100          105          110
Leu Gln Glu Leu Cys Trp Glu Tyr Ser Asp Tyr Asn Ile Lys Leu Cys
          115          120          125
Glu Asp Ala val Leu Asn Lys Lys Leu Met Arg Lys Leu Gln Glu Ser
          130          135          140

```

## SEQUENCE LISTING 1657-2022.txt

Lys Phe Asp Val Leu Leu Ala Asp Ala Val Asn Pro Cys Gly Glu Leu  
 145 150 155 160  
 Leu Ala Glu Leu Leu Asn Ile Pro Phe Leu Tyr Ser Leu Arg Phe Ser  
 165 170 175  
 Val Gly Tyr Thr Val Glu Lys Asn Gly Gly Gly Phe Leu Phe Pro Pro  
 180 185 190  
 Ser Tyr Val Pro Val Val Met Ser Glu Leu Ser Asp Gln Met Ile Phe  
 195 200 205  
 Met Glu Arg Ile Lys Asn Met Ile Tyr Met Leu Tyr Phe Asp Phe Trp  
 210 215 220  
 Phe Gln Ala Tyr Asp Leu Lys Lys Trp Asp Gln Phe Tyr Ser Glu Val  
 225 230 235 240  
 Leu Gly Arg Pro Thr Thr Leu Phe Glu Thr Met Gly Lys Ala Glu Met  
 245 250 255  
 Trp Leu Ile Arg Thr Tyr Trp Asp Phe Glu Phe Pro Arg Pro Phe Leu  
 260 265 270  
 Pro Asn Val Asp Phe Val Gly Gly Leu His Cys Lys Pro Ala Lys Pro  
 275 280 285  
 Leu Pro Lys Glu Met Glu Glu Phe Val Gln Ser Ser Gly Glu Asn Gly  
 290 295 300  
 Ile Val Val Phe Ser Leu Gly Ser Met Ile Ser Asn Met Ser Glu Glu  
 305 310 315 320  
 Ser Ala Asn Met Ile Ala Ser Ala Leu Ala Gln Ile Pro Gln Lys Val  
 325 330 335  
 Leu Trp Arg Phe Asp Gly Lys Lys Pro Asn Thr Leu Gly Ser Asn Thr  
 340 345 350  
 Arg Leu Tyr Lys Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro Lys  
 355 360 365  
 Thr Lys Ala Phe Ile Thr His Gly Gly Thr Asn Gly Ile Tyr Glu Ala  
 370 375 380  
 Ile Tyr His Gly Ile Pro Met Val Gly Ile Pro Leu Phe Ala Asp Gln  
 385 390 395 400  
 His Asp Asn Ile Ala His Met Lys Ala Lys Gly Ala Ala Leu Ser Val  
 405 410 415  
 Asp Ile Arg Thr Met Ser Ser Arg Asp Leu Leu Asn Ala Leu Lys Ser  
 420 425 430  
 Val Ile Asn Asp Pro Ile Tyr Lys Glu Asn Ile Met Lys Leu Ser Arg  
 435 440 445  
 Ile His His Asp Gln Pro Val Lys Pro Leu Asp Arg Ala Val Phe Trp  
 450 455 460  
 Ile Glu Phe Val Met Arg His Lys Gly Ala Lys His Leu Arg Val Ala  
 465 470 475 480  
 Ala His Asn Leu Thr Trp Ile Gln Tyr His Ser Leu Asp Val Ile Ala  
 485 490 495  
 Phe Leu Leu Ala Cys Val Ala Thr Met Ile Phe Met Ile Thr Lys Cys  
 500 505 510  
 Cys Leu Phe Cys Phe Arg Lys Leu Ala Lys Thr Gly Lys Lys Lys Lys  
 515 520 525  
 Arg Asp  
 530

<210> 166  
 <211> 387  
 <212> PRT  
 <213> Homo sapiens

<400> 166  
 Met Ser Thr Phe Phe Ser Asp Thr Ala Trp Ile Cys Leu Ala Val Pro  
 1 5 10 15  
 Thr Val Leu Cys Gly Thr Val Phe Cys Lys Tyr Lys Lys Ser Ser Gly  
 20 25 30  
 Gln Leu Trp Ser Trp Met Val Cys Leu Ala Gly Leu Cys Ala Val Cys  
 35 40 45  
 Leu Leu Ile Leu Ser Pro Phe Trp Gly Leu Ile Leu Phe Ser Val Ser  
 50 55 60  
 Cys Phe Leu Met Tyr Thr Tyr Leu Ser Gly Gln Glu Leu Leu Pro Val  
 Page 153

## SEQUENCE LISTING 1657-2022.txt

```

65      70      75      80
Asp Gln Lys Ala Val Leu Val Thr Gly Gly Asp Cys Gly Leu Gly His
      85
Ala Leu Cys Lys Tyr Leu Asp Glu Leu Gly Phe Thr Val Phe Ala Gly
      100
Val Leu Asn Glu Asn Gly Pro Gly Ala Glu Glu Leu Arg Arg Thr Cys
      115
Ser Pro Arg Leu Ser Val Leu Gln Met Asp Ile Thr Lys Pro Val Gln
      130
Ile Lys Asp Ala Tyr Ser Lys Val Ala Ala Met Leu Gln Asp Arg Gly
      145
Leu Trp Ala Val Ile Asn Asn Ala Gly Val Leu Gly Phe Pro Thr Asp
      165
Gly Glu Leu Leu Leu Met Thr Asp Tyr Lys Gln Cys Met Ala Val Asn
      180
Phe Phe Gly Thr Val Glu Val Thr Lys Thr Phe Leu Pro Leu Leu Arg
      195
Lys Ser Lys Gly Arg Leu Val Asn Val Ser Ser Met Gly Gly Ala
      210
Pro Met Glu Arg Leu Ala Ser Tyr Gly Ser Ser Lys Ala Ala Val Thr
      225
Met Phe Ser Ser Val Met Arg Leu Glu Leu Ser Lys Trp Gly Ile Lys
      245
Val Ala Ser Ile Gln Pro Gly Gly Phe Leu Thr Asn Ile Ala Gly Thr
      260
Ser Asp Lys Trp Glu Lys Leu Glu Lys Asp Ile Leu Asp His Leu Pro
      275
Ala Glu Val Gln Glu Asp Tyr Gly Gln Asp Tyr Ile Leu Ala Gln Arg
      290
Asn Phe Leu Leu Leu Ile Asn Ser Leu Ala Ser Lys Asp Phe Ser Pro
      305
Val Leu Arg Asp Ile Gln His Ala Ile Leu Ala Lys Ser Pro Phe Ala
      325
Tyr Tyr Thr Pro Gly Lys Gly Ala Tyr Leu Trp Ile Cys Leu Ala His
      340
Tyr Leu Pro Ile Gly Ile Tyr Asp Tyr Phe Ala Lys Arg His Phe Gly
      355
Gln Asp Lys Pro Met Pro Arg Ala Leu Arg Met Pro Asn Tyr Lys Lys
      370
Lys Ala Thr
      385

```

&lt;210&gt; 167

&lt;211&gt; 196

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 167

```

Met Gly Ser Arg Ser Ser His Ala Ala Val Ile Pro Asp Gly Asp Ser
1      5      10      15
Ile Arg Arg Glu Thr Gly Phe Ser Gln Ala Ser Leu Leu Arg Leu His
      20
His Arg Phe Arg Ala Leu Asp Arg Asn Lys Lys Gly Tyr Leu Ser Arg
      35
Met Asp Leu Gln Gln Ile Gly Ala Leu Ala Val Asn Pro Leu Gly Asp
      50
Arg Ile Ile Glu Ser Phe Phe Pro Asp Gly Ser Gln Arg Val Asp Phe
      65
Pro Gly Phe Val Arg Val Leu Ala His Phe Arg Pro Val Glu Asp Glu
      85
Asp Thr Glu Thr Gln Asp Pro Lys Lys Pro Glu Pro Leu Asn Ser Arg
      100
Arg Asn Lys Leu His Tyr Ala Phe Gln Leu Tyr Asp Leu Asp Arg Asp
      115
Gly Lys Ile Ser Arg His Glu Met Leu Gln Val Leu Arg Leu Met Val
      130
      135
      140

```

## SEQUENCE LISTING 1657-2022.txt

Gly Val Gln Val Thr Glu Glu Gln Leu Glu Asn Ile Ala Asp Arg Thr  
 145 150 155 160  
 Val Gln Glu Ala Asp Glu Asp Gly Asp Gly Ala Val Ser Phe Val Glu  
 165 170 175  
 Phe Thr Lys Ser Leu Glu Lys Met Asp Val Glu Gln Lys Met Ser Ile  
 180 185 190  
 Arg Ile Leu Lys  
 195

<210> 168  
 <211> 319  
 <212> PRT  
 <213> Homo sapiens

<400> 168  
 Met Leu Phe Trp Val Leu Gly Leu Leu Ile Leu Cys Gly Phe Leu Trp  
 1 5 10 15  
 Thr Arg Lys Gly Lys Leu Lys Ile Glu Asp Ile Thr Asp Lys Tyr Ile  
 20 25 30  
 Phe Ile Thr Gly Cys Asp Ser Gly Phe Gly Asn Leu Ala Ala Arg Thr  
 35 40 45  
 Phe Asp Lys Lys Gly Phe His Val Ile Ala Ala Cys Leu Thr Glu Ser  
 50 55 60  
 Gly Ser Thr Ala Leu Lys Ala Glu Thr Ser Glu Arg Leu Arg Thr Val  
 65 70 75 80  
 Leu Leu Asp Val Thr Asp Pro Glu Asn Val Lys Arg Thr Ala Gln Trp  
 85 90 95  
 Val Lys Asn Gln Val Gly Glu Lys Gly Leu Trp Gly Leu Ile Asn Asn  
 100 105 110  
 Ala Gly Val Pro Gly Val Leu Ala Pro Thr Asp Trp Leu Thr Leu Glu  
 115 120 125  
 Asp Tyr Arg Glu Pro Ile Glu Val Asn Leu Phe Gly Leu Ile Ser Val  
 130 135 140  
 Thr Leu Asn Met Leu Pro Leu Val Lys Lys Ala Gln Gly Arg Val Ile  
 145 150 155 160  
 Asn Val Ser Ser Val Gly Gly Arg Leu Ala Ile Val Gly Gly Gly Tyr  
 165 170 175  
 Thr Pro Ser Lys Tyr Ala Val Glu Gly Phe Asn Asp Ser Leu Arg Arg  
 180 185 190  
 Asp Met Lys Ala Phe Gly Val His Val Ser Cys Ile Glu Pro Gly Leu  
 195 200 205  
 Phe Lys Thr Asn Leu Ala Asp Pro Val Lys Val Ile Glu Lys Lys Leu  
 210 215 220  
 Ala Ile Trp Glu Gln Leu Ser Pro Asp Ile Lys Gln Gln Tyr Gly Glu  
 225 230 235 240  
 Gly Tyr Ile Glu Lys Ser Leu Asp Lys Leu Lys Gly Asn Lys Ser Tyr  
 245 250 255  
 Val Asn Met Asp Leu Ser Pro Val Val Glu Cys Met Asp His Ala Leu  
 260 265 270  
 Thr Ser Leu Phe Pro Lys Thr His Tyr Ala Ala Gly Lys Asp Ala Lys  
 275 280 285  
 Ile Phe Trp Ile Pro Leu Ser His Met Pro Ala Ala Leu Gln Asp Phe  
 290 295 300  
 Leu Leu Leu Lys Gln Lys Ala Glu Leu Ala Asn Pro Lys Ala Val  
 305 310 315

<210> 169  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens

<400> 169  
 Met Gly Gln Glu Phe Ser Trp Glu Glu Ala Glu Ala Ala Gly Glu Ile  
 1 5 10 15  
 Asp Val Ala Glu Leu Gln Glu Trp Tyr Lys Lys Phe Val Met Glu Cys  
 Page 155

## SEQUENCE LISTING 1657-2022.txt

```

      20      25      30
Pro Ser Gly Thr Leu Phe Met His Glu Phe Lys Arg Phe Phe Lys Val
      35      40      45
Thr Asp Asp Glu Glu Ala Ser Gln Tyr Val Glu Gly Met Phe Arg Ala
      50      55      60
Phe Asp Lys Asn Gly Asp Asn Thr Ile Asp Phe Leu Glu Tyr Val Ala
      65      70      75      80
Ala Leu Asn Leu Val Leu Arg Gly Thr Leu Glu His Lys Leu Lys Trp
      85      90      95
Thr Phe Lys Ile Tyr Asp Lys Asp Gly Asn Gly Cys Ile Asp Arg Leu
      100      105      110
Glu Leu Leu Asn Ile Val Glu Gly Ile Tyr Gln Leu Lys Lys Ala Cys
      115      120      125
Arg Arg Glu Leu Gln Thr Glu Gln Asp Gln Leu Leu Thr Pro Glu Glu
      130      135      140
Val Val Asp Arg Ile Phe Leu Leu Val Asp Glu Asn Gly Asp Gly Gln
      145      150      155      160
Leu Ser Leu Asn Glu Phe Val Glu Gly Ala Arg Arg Asp Lys Trp Val
      165      170      175
Met Lys Met Leu Gln Met Asp Met Asn Pro Ser Ser Trp Leu Ala Gln
      180      185      190
Gln Arg Arg Lys Ser Ala Met Phe
      195      200

```

<210> 170  
 <211> 280  
 <212> PRT  
 <213> Homo sapiens

```

<400> 170
Met Ala Glu Lys Phe Asp Cys His Tyr Cys Arg Asp Pro Leu Gln Gly
  1      5      10      15
Lys Lys Tyr Val Gln Lys Asp Gly His His Cys Cys Leu Lys Cys Phe
      20      25      30
Asp Lys Phe Cys Ala Asn Thr Cys Val Glu Cys Arg Lys Pro Ile Gly
      35      40      45
Ala Asp Ser Lys Glu Val His Tyr Lys Asn Arg Phe Trp His Asp Thr
      50      55      60
Cys Phe Arg Cys Ala Lys Cys Leu His Pro Leu Ala Asn Glu Thr Phe
      65      70      75      80
Val Ala Lys Asp Asn Lys Ile Leu Cys Asn Lys Cys Thr Thr Arg Glu
      85      90      95
Asp Ser Pro Lys Cys Lys Gly Cys Phe Lys Ala Ile Val Ala Gly Asp
      100      105      110
Gln Asn Val Glu Tyr Lys Gly Thr Val Trp His Lys Asp Cys Phe Thr
      115      120      125
Cys Ser Asn Cys Lys Gln Val Ile Gly Thr Gly Ser Phe Phe Pro Lys
      130      135      140
Gly Glu Asp Phe Tyr Cys Val Thr Cys His Glu Thr Lys Phe Ala Lys
      145      150      155      160
His Cys Val Lys Cys Asn Lys Ala Ile Thr Ser Gly Gly Ile Thr Tyr
      165      170      175
Gln Asp Gln Pro Trp His Ala Asp Cys Phe Val Cys Val Thr Cys Ser
      180      185      190
Lys Lys Leu Ala Gly Gln Arg Phe Thr Ala Val Glu Asp Gln Tyr Tyr
      195      200      205
Cys Val Asp Cys Tyr Lys Asn Phe Val Ala Lys Lys Cys Ala Gly Cys
      210      215      220
Lys Asn Pro Ile Thr Gly Phe Gly Lys Gly Ser Ser Val Val Ala Tyr
      225      230      235      240
Glu Gly Gln Ser Trp His Asp Tyr Cys Phe His Cys Lys Lys Cys Ser
      245      250      255
Val Asn Leu Ala Asn Lys Arg Phe Val Phe His Gln Glu Gln Val Tyr
      260      265      270
Cys Pro Asp Cys Ala Lys Lys Leu
      275      280

```

## SEQUENCE LISTING 1657-2022.txt

<210> 171  
 <211> 470  
 <212> PRT  
 <213> Homo sapiens

<400> 171

```

Met Leu Arg Gly Ile Ser Gln Leu Pro Ala Val Ala Thr Met Ser Trp
1      5      10      15
Val Leu Leu Pro Val Leu Trp Leu Ile Val Gln Thr Gln Ala Ile Ala
20      25      30
Ile Lys Gln Thr Pro Glu Leu Thr Leu His Glu Ile Val Cys Pro Lys
35      40      45
Lys Leu His Ile Leu His Lys Arg Glu Ile Lys Asn Asn Gln Thr Glu
50      55      60
Lys His Gly Lys Glu Glu Arg Tyr Glu Pro Glu Val Gln Tyr Gln Met
65      70      75      80
Ile Leu Asn Gly Glu Glu Ile Ile Leu Ser Leu Gln Lys Thr Lys His
85      90      95
Leu Leu Gly Pro Asp Tyr Thr Glu Thr Leu Tyr Ser Pro Arg Gly Glu
100     105     110
Glu Ile Thr Thr Lys Pro Glu Asn Met Glu His Cys Tyr Tyr Lys Gly
115     120     125
Asn Ile Leu Asn Glu Lys Asn Ser Val Ala Ser Ile Ser Thr Cys Asp
130     135     140
Gly Leu Arg Gly Tyr Phe Thr His His His Gln Arg Tyr Gln Ile Lys
145     150     155     160
Pro Leu Lys Ser Thr Asp Glu Lys Glu His Ala Val Phe Thr Ser Asn
165     170     175
Gln Glu Glu Gln Asp Pro Ala Asn His Thr Cys Gly Val Lys Ser Thr
180     185     190
Asp Gly Lys Gln Gly Pro Ile Arg Ile Ser Arg Ser Leu Lys Ser Pro
195     200     205
Glu Lys Glu Asp Phe Leu Arg Ala Gln Lys Tyr Ile Asp Leu Tyr Leu
210     215     220
Val Leu Asp Asn Ala Phe Tyr Lys Asn Tyr Asn Glu Asn Leu Thr Leu
225     230     235     240
Ile Arg Ser Phe Val Phe Asp Val Met Asn Leu Leu Asn Val Ile Tyr
245     250     255
Asn Thr Ile Asp Val Gln Val Ala Leu Val Gly Met Glu Ile Trp Ser
260     265     270
Asp Gly Asp Lys Ile Lys Val Val Pro Ser Ala Ser Thr Thr Phe Asp
275     280     285
Asn Phe Leu Arg Trp His Ser Ser Asn Leu Gly Lys Lys Ile His Asp
290     295     300
His Ala Gln Leu Leu Ser Gly Ile Ser Phe Asn Asn Arg Arg Val Gly
305     310     315     320
Leu Ala Ala Ser Asn Ser Leu Cys Ser Pro Ser Ser Val Ala Val Ile
325     330     335
Glu Ala Lys Lys Lys Asn Asn Val Ala Leu Val Gly Val Met Ser His
340     345     350
Glu Leu Gly His Val Leu Gly Met Pro Asp Val Pro Phe Asn Thr Lys
355     360     365
Cys Pro Ser Gly Ser Cys Val Met Asn Gln Tyr Leu Ser Ser Lys Phe
370     375     380
Pro Lys Asp Phe Ser Thr Ser Cys Arg Ala His Phe Glu Arg Tyr Leu
385     390     395     400
Leu Ser Gln Lys Pro Lys Cys Leu Leu Gln Ala Pro Ile Pro Thr Asn
405     410     415
Ile Met Thr Thr Pro Val Cys Gly Asn His Leu Leu Glu Val Gly Glu
420     425     430
Asp Cys Asp Cys Gly Ser Pro Lys Glu Cys Thr Asn Leu Cys Cys Glu
435     440     445
Ala Leu Thr Cys Lys Leu Lys Pro Gly Thr Asp Cys Gly Gly Asp Ala
450     455     460
Pro Asn His Thr Thr Glu

```

## SEQUENCE LISTING 1657-2022.txt

465

470

<210> 172  
 <211> 86  
 <212> PRT  
 <213> Homo sapiens

<400> 172  
 Met Ala Val Arg Gln Trp Val Ile Ala Leu Ala Leu Ala Ala Leu Leu  
 1 5 10 15  
 Val Val Asp Arg Glu Val Pro Val Ala Ala Gly Lys Leu Pro Phe Ser  
 20 25 30  
 Arg Met Pro Ile Cys Glu His Met Val Glu Ser Pro Thr Cys Ser Gln  
 35 40 45  
 Met Ser Asn Leu Val Cys Gly Thr Asp Gly Leu Thr Tyr Thr Asn Glu  
 50 55 60  
 Cys Gln Leu Cys Leu Ala Arg Ile Lys Thr Lys Gln Asp Ile Gln Ile  
 65 70 75 80  
 Met Lys Asp Gly Lys Cys  
 85

<210> 173  
 <211> 261  
 <212> PRT  
 <213> Homo sapiens

<400> 173  
 Met Ala Ser Pro Asp Trp Gly Tyr Asp Asp Lys Asn Gly Pro Glu Gln  
 1 5 10 15  
 Trp Ser Lys Leu Tyr Pro Ile Ala Asn Gly Asn Asn Gln Ser Pro Val  
 20 25 30  
 Asp Ile Lys Thr Ser Glu Thr Lys His Asp Thr Ser Leu Lys Pro Ile  
 35 40 45  
 Ser Val Ser Tyr Asn Pro Ala Thr Ala Lys Glu Ile Ile Asn Val Gly  
 50 55 60  
 His Ser Phe His Val Asn Phe Glu Asp Asn Asp Asn Arg Ser Val Leu  
 65 70 75 80  
 Lys Gly Gly Pro Phe Ser Asp Ser Tyr Arg Leu Phe Gln Phe His Phe  
 85 90 95  
 His Trp Gly Ser Thr Asn Glu His Gly Ser Glu His Thr Val Asp Gly  
 100 105 110  
 Val Lys Tyr Ser Ala Glu Leu His Val Ala His Trp Asn Ser Ala Lys  
 115 120 125  
 Tyr Ser Ser Leu Ala Glu Ala Ala Ser Lys Ala Asp Gly Leu Ala Val  
 130 135 140  
 Ile Gly Val Leu Met Lys Val Gly Glu Ala Asn Pro Lys Leu Gln Lys  
 145 150 155 160  
 Val Leu Asp Ala Leu Gln Ala Ile Lys Thr Lys Gly Lys Arg Ala Pro  
 165 170 175  
 Phe Thr Asn Phe Asp Pro Ser Thr Leu Leu Pro Ser Ser Leu Asp Phe  
 180 185 190  
 Trp Thr Tyr Pro Gly Ser Leu Thr His Pro Pro Leu Tyr Glu Ser Val  
 195 200 205  
 Thr Trp Ile Ile Cys Lys Glu Ser Ile Ser Val Ser Ser Glu Gln Leu  
 210 215 220  
 Ala Gln Phe Arg Ser Leu Leu Ser Asn Val Glu Gly Asp Asn Ala Val  
 225 230 235 240  
 Pro Met Gln His Asn Asn Arg Pro Thr Gln Pro Leu Lys Gly Arg Thr  
 245 250 255  
 Val Arg Ala Ser Phe  
 260

<210> 174  
 <211> 431



## SEQUENCE LISTING 1657-2022.txt

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 174

```

Met Thr Val Lys Thr Glu Ala Ala Lys Gly Thr Leu Thr Tyr Ser Arg
1      5      10      15
Met Arg Gly Met Val Ala Ile Leu Ile Ala Phe Met Lys Gln Arg Arg
20      25      30
Met Gly Leu Asn Asp Phe Ile Gln Lys Ile Ala Asn Asn Ser Tyr Ala
35      40      45
Cys Lys His Pro Glu Val Gln Ser Ile Leu Lys Ile Ser Gln Pro Gln
50      55      60
Glu Pro Glu Leu Met Asn Ala Asn Pro Ser Pro Pro Ser Pro Ser
65      70      75      80
Gln Gln Ile Asn Leu Gly Pro Ser Ser Asn Pro His Ala Lys Pro Ser
85      90      95
Asp Phe His Phe Leu Lys Val Ile Gly Lys Gly Ser Phe Gly Lys Val
100      105      110
Leu Leu Ala Arg His Lys Ala Glu Glu Val Phe Tyr Ala Val Lys Val
115      120      125
Leu Gln Lys Lys Ala Ile Leu Lys Lys Lys Glu Glu Lys His Ile Met
130      135      140
Ser Glu Arg Asn Val Leu Leu Lys Asn Val Lys His Pro Phe Leu Val
145      150      155      160
Gly Leu His Phe Ser Phe Gln Thr Ala Asp Lys Leu Tyr Phe Val Leu
165      170      175
Asp Tyr Ile Asn Gly Gly Glu Leu Phe Tyr His Leu Gln Arg Glu Arg
180      185      190
Cys Phe Leu Glu Pro Arg Ala Arg Phe Tyr Ala Ala Glu Ile Ala Ser
195      200      205
Ala Leu Gly Tyr Leu His Ser Leu Asn Ile Val Tyr Arg Asp Leu Lys
210      215      220
Pro Glu Asn Ile Leu Leu Asp Ser Gln Gly His Ile Val Leu Thr Asp
225      230      235      240
Phe Gly Leu Cys Lys Glu Asn Ile Glu His Asn Ser Thr Thr Ser Thr
245      250      255
Phe Cys Gly Thr Pro Glu Tyr Leu Ala Pro Glu Val Leu His Lys Gln
260      265      270
Pro Tyr Asp Arg Thr Val Asp Trp Trp Cys Leu Gly Ala Val Leu Tyr
275      280      285
Glu Met Leu Tyr Gly Leu Pro Phe Tyr Ser Arg Asn Thr Ala Glu
290      295      300
Met Tyr Asp Asn Ile Leu Asn Lys Pro Leu Gln Leu Lys Pro Asn Ile
305      310      315      320
Thr Asn Ser Ala Arg His Leu Leu Glu Gly Leu Leu Gln Lys Asp Arg
325      330      335
Thr Lys Arg Leu Gly Ala Lys Asp Asp Phe Met Glu Ile Lys Ser His
340      345      350
Val Phe Phe Ser Leu Ile Asn Trp Asp Asp Leu Ile Asn Lys Lys Ile
355      360      365
Thr Pro Pro Phe Asn Pro Asn Val Ser Gly Pro Asn Asp Leu Arg His
370      375      380
Phe Asp Pro Glu Phe Thr Glu Glu Pro Val Pro Asn Ser Ile Gly Lys
385      390      395      400
Ser Pro Asp Ser Val Leu Val Thr Ala Ser Val Lys Glu Ala Ala Glu
405      410      415
Ala Phe Leu Gly Phe Ser Tyr Ala Pro Thr Asp Ser Phe Leu
420      425      430

```

&lt;210&gt; 175

&lt;211&gt; 381

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 175

Met Pro Phe Ser Asn Ser His Asn Ala Leu Lys Leu Arg Phe Pro Ala

## SEQUENCE LISTING 1657-2022.txt

```

1      5      10      15
Glu Asp Glu Phe Pro Asp Leu Ser Ala His Asn Asn His Met Ala Lys
20      25      30
Val Leu Thr Pro Glu Leu Tyr Ala Glu Leu Arg Ala Lys Ser Thr Pro
35      40      45
Ser Gly Phe Thr Leu Asp Asp Val Ile Gln Thr Gly Val Asp Asn Pro
50      55      60
Gly His Pro Tyr Ile Met Thr Val Gly Cys Val Ala Gly Asp Glu Glu
65      70      75      80
Ser Tyr Glu Val Phe Lys Asp Leu Phe Asp Pro Ile Ile Glu Asp Arg
85      90      95
His Gly Gly Tyr Lys Pro Ser Asp Glu His Lys Thr Asp Leu Asn Pro
100     105     110
Asp Asn Leu Gln Gly Gly Asp Asp Leu Asp Pro Asn Tyr Val Leu Ser
115     120     125
Ser Arg Val Arg Thr Gly Arg Ser Ile Arg Gly Phe Cys Leu Pro Pro
130     135     140
His Cys Ser Arg Gly Glu Arg Arg Ala Ile Glu Lys Leu Ala Val Glu
145     150     155     160
Ala Leu Ser Ser Leu Asp Gly Asp Leu Ala Gly Arg Tyr Tyr Ala Leu
165     170     175
Lys Ser Met Thr Glu Ala Glu Gln Gln Gln Leu Ile Asp Asp His Phe
180     185     190
Leu Phe Asp Lys Pro Val Ser Pro Leu Leu Leu Ala Ser Gly Met Ala
195     200     205
Arg Asp Trp Pro Asp Ala Arg Gly Ile Trp His Asn Asp Asn Lys Thr
210     215     220
Phe Leu Val Trp Val Asn Glu Glu Asp His Leu Arg Val Ile Ser Met
225     230     235     240
Gln Lys Gly Gly Asn Met Lys Glu Val Phe Thr Arg Phe Cys Thr Gly
245     250     255
Leu Thr Gln Ile Glu Thr Leu Phe Lys Ser Lys Asp Tyr Glu Phe Met
260     265     270
Trp Asn Pro His Leu Gly Tyr Ile Leu Thr Cys Pro Ser Asn Leu Gly
275     280     285
Thr Gly Leu Arg Ala Gly Val His Ile Lys Leu Pro Asn Leu Gly Lys
290     295     300
His Glu Lys Phe Ser Glu Val Leu Lys Arg Leu Arg Leu Gln Lys Arg
305     310     315     320
Gly Thr Gly Gly Val Asp Thr Ala Ala Val Gly Gly Val Phe Asp Val
325     330     335
Ser Asn Ala Asp Arg Leu Gly Phe Ser Glu Val Glu Leu Val Gln Met
340     345     350
Val Val Asp Gly Val Lys Leu Leu Ile Glu Met Glu Gln Arg Leu Glu
355     360     365
Gln Gly Gln Ala Ile Asp Asp Leu Met Pro Ala Gln Lys
370     375     380

```

&lt;210&gt; 176

&lt;211&gt; 739

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 176

```

Met Ser Ser Glu Ser Lys Glu Gln His Asn Val Ser Pro Arg Asp Ser
1      5      10      15
Ala Glu Gly Asn Asp Ser Tyr Pro Ser Gly Ile His Leu Glu Leu Gln
20      25      30
Arg Glu Ser Ser Thr Asp Phe Lys Gln Phe Glu Thr Asn Asp Gln Cys
35      40      45
Arg Pro Tyr His Arg Ile Leu Ile Glu Arg Gln Glu Lys Ser Asp Thr
50      55      60
Asn Phe Lys Glu Phe Val Ile Lys Lys Leu Gln Lys Asn Cys Gln Cys
65      70      75      80
Ser Pro Ala Lys Ala Lys Asn Met Ile Leu Gly Phe Leu Pro Val Leu
85      90      95

```

## SEQUENCE LISTING 1657-2022.txt

Gln Trp Leu Pro Lys Tyr Asp Leu Lys Lys Asn Ile Leu Gly Asp Val  
 100 105 110  
 Met Ser Gly Leu Ile Val Gly Ile Leu Leu Val Pro Gln Ser Ile Ala  
 115 120 125  
 Tyr Ser Leu Leu Ala Gly Gln Glu Pro Val Tyr Gly Leu Tyr Thr Ser  
 130 135 140  
 Phe Phe Ala Ser Ile Ile Tyr Phe Leu Leu Gly Thr Ser Arg His Ile  
 145 150 155 160  
 Ser Val Gly Ile Phe Gly Val Leu Cys Leu Met Ile Gly Glu Thr Val  
 165 170 175  
 Asp Arg Glu Leu Gln Lys Ala Gly Tyr Asp Asn Ala His Ser Ala Pro  
 180 185 190  
 Ser Leu Gly Met Val Ser Asn Gly Ser Thr Leu Leu Asn His Thr Ser  
 195 200 205  
 Asp Arg Ile Cys Asp Lys Ser Cys Tyr Ala Ile Met Val Gly Ser Thr  
 210 215 220  
 Val Thr Phe Ile Ala Gly Val Tyr Gln Val Ala Met Gly Phe Phe Gln  
 225 230 235 240  
 Val Gly Phe Val Ser Val Tyr Leu Ser Asp Ala Leu Leu Ser Gly Phe  
 245 250 255  
 Val Thr Gly Ala Ser Phe Thr Ile Leu Thr Ser Gln Ala Lys Tyr Leu  
 260 265 270  
 Leu Gly Leu Asn Leu Pro Arg Thr Asn Gly Val Gly Ser Leu Ile Thr  
 275 280 285  
 Thr Trp Ile His Val Phe Arg Asn Ile His Lys Thr Asn Leu Cys Asp  
 290 295 300  
 Leu Ile Thr Ser Leu Leu Cys Leu Leu Val Leu Leu Pro Thr Lys Glu  
 305 310 315 320  
 Leu Asn Glu His Phe Lys Ser Lys Leu Lys Ala Pro Ile Pro Ile Glu  
 325 330 335  
 Leu Val Val Val Val Ala Ala Thr Leu Ala Ser His Phe Gly Lys Leu  
 340 345 350  
 His Glu Asn Tyr Asn Ser Ser Ile Ala Gly His Ile Pro Thr Gly Phe  
 355 360 365  
 Met Pro Pro Lys Val Pro Glu Trp Asn Leu Ile Pro Ser Val Ala Val  
 370 375 380  
 Asp Ala Ile Ala Ile Ser Ile Ile Gly Phe Ala Ile Thr Val Ser Leu  
 385 390 395 400  
 Ser Glu Met Phe Ala Lys Lys His Gly Tyr Thr Val Lys Ala Asn Gln  
 405 410 415  
 Glu Met Tyr Ala Ile Gly Phe Cys Asn Ile Ile Pro Ser Phe Phe His  
 420 425 430  
 Cys Phe Thr Thr Ser Ala Ala Leu Ala Lys Thr Leu Val Lys Glu Ser  
 435 440 445  
 Thr Gly Cys His Thr Gln Leu Ser Gly Val Val Thr Ala Leu Val Leu  
 450 455 460  
 Leu Leu Val Leu Leu Val Ile Ala Pro Leu Phe Tyr Ser Leu Gln Lys  
 465 470 475 480  
 Ser Val Leu Gly Val Ile Thr Ile Val Asn Leu Arg Gly Ala Leu Arg  
 485 490 495  
 Lys Phe Arg Asp Leu Pro Lys Met Trp Ser Ile Ser Arg Met Asp Thr  
 500 505 510  
 Val Ile Trp Phe Val Thr Met Leu Ser Ser Ala Leu Leu Ser Thr Glu  
 515 520 525  
 Ile Gly Leu Leu Val Gly Val Cys Phe Ser Ile Phe Cys Val Ile Leu  
 530 535 540  
 Arg Thr Gln Lys Pro Lys Ser Ser Leu Leu Gly Leu Val Glu Glu Ser  
 545 550 555 560  
 Glu Val Phe Glu Ser Val Ser Ala Tyr Lys Asn Leu Gln Thr Lys Pro  
 565 570 575  
 Gly Ile Lys Ile Phe Arg Phe Val Ala Pro Leu Tyr Tyr Ile Asn Lys  
 580 585 590  
 Glu Cys Phe Lys Ser Ala Leu Tyr Lys Gln Thr Val Asn Pro Ile Leu  
 595 600 605  
 Ile Lys Val Ala Trp Lys Lys Ala Ala Lys Arg Lys Ile Lys Glu Lys  
 610 615 620  
 Val Val Thr Leu Gly Gly Ile Gln Asp Glu Met Ser Val Gln Leu Ser

SEQUENCE LISTING 1657-2022.txt															
625					630					635					640
His	Asp	Pro	Leu	Glu	Leu	His	Thr	Ile	Val	Ile	Asp	Cys	Ser	Ala	Ile
Gln	Phe	Leu	Asp	Thr	Ala	Gly	Ile	His	Thr	Leu	Lys	Glu	Val	Arg	Arg
Asp	Tyr	Glu	Ala	Ile	Gly	Ile	Gln	Val	Leu	Leu	Ala	Gln	Cys	Asn	Pro
Thr	Val	Arg	Asp	Ser	Leu	Thr	Asn	Gly	Glu	Tyr	Cys	Lys	Lys	Glu	Glu
Glu	Asn	Leu	Leu	Phe	Tyr	Ser	Val	Tyr	Glu	Ala	Met	Ala	Phe	Ala	Glu
Val	Ser	Lys	Asn	Gln	Lys	Gly	Val	Cys	Val	Pro	Asn	Gly	Leu	Ser	Leu
Ser	Ser	Asp													

```
<210> 177
<211> 709
<212> PRT
<213> Homo sapiens
```

<400> 177

Met 1	Ala 17	Glu 18	Val 19	Glu 5	Asp 6	Gln 7	Ala 8	Ala 9	Arg 10	Asp 11	Met 12	Lys 13	Arg 14	Leu 15	Glu 16
Glu 20	Lys 21	Asp 22	Lys 23	Glu 24	Arg 25	Lys 26	Asn 27	Val 28	Lys 29	Gly 30	Ile 31	Arg 32	Asp 33	Asp 34	Ile 35
Glu 36	Glu 37	Glu 38	Asp 39	Asp 40	Gln 41	Glu 42	Ala 43	Tyr 44	Phe 45	Arg 46	Tyr 47	Met 48	Ala 49	Glu 50	Asn 51
Pro 52	Thr 53	Ala 54	Gly 55	Val 56	Val 57	Gln 58	Glu 59	Glu 60	Glu 61	Glu 62	Asp 63	Asn 64	Leu 65	Glu 66	Tyr 67
Asp 68	Ser 69	Asp 70	Gly 71	Asn 72	Pro 73	Ile 74	Ala 75	Pro 76	Thr 77	Lys 78	Lys 79	Ile 80	Ile 81	Asp 82	Pro 83
Leu 84	Pro 85	Pro 86	Ile 87	Asp 88	His 89	Ser 90	Glu 91	Ile 92	Asp 93	Tyr 94	Pro 95	Pro 96	Phe 97	Glu 98	Lys 99
Asn 100	Phe 101	Tyr 102	Asn 103	Glu 104	His 105	Glu 106	Glu 107	Ile 108	Thr 109	Asn 110	Leu 111	Thr 112	Pro 113	Gln 114	Gln 115
Leu 116	Ile 117	Asp 118	Leu 119	Arg 120	His 121	Lys 122	Leu 123	Asn 124	Leu 125	Arg 126	Val 127	Ser 128	Gly 129	Ala 130	Ala 131
Pro 132	Pro 133	Arg 134	Pro 135	Gly 136	Ser 137	Ser 138	Phe 139	Ala 140	His 141	Phe 142	Gly 143	Phe 144	Asp 145	Glu 146	Gln 147
Leu 148	Met 149	His 150	Gln 151	Ile 152	Arg 153	Lys 154	Ser 155	Glu 156	Tyr 157	Thr 158	Gln 159	Pro 160	Thr 161	Pro 162	Ile 163
Gln 164	Cys 165	Gln 166	Gly 167	Val 168	Pro 169	Val 170	Ala 171	Leu 172	Ser 173	Gly 174	Arg 175	Asp 176	Met 177	Ile 178	Gly 179
Ile 180	Ala 181	Lys 182	Thr 183	Gly 184	Ser 185	Gly 186	Lys 187	Thr 188	Ala 189	Ala 190	Phe 191	Ile 192	Trp 193	Pro 194	Met 195
Leu 196	Ile 197	His 198	Ile 199	Met 200	Asp 201	Gln 202	Lys 203	Glu 204	Leu 205	Glu 206	Pro 207	Gly 208	Asp 209	Gly 210	Pro 211
Ile 212	Ala 213	Val 214	Ile 215	Val 216	Cys 217	Pro 218	Thr 219	Arg 220	Glu 221	Leu 222	Cys 223	Gln 224	Gln 225	Ile 226	His 227
Ala 228	Glu 229	Cys 230	Lys 231	Arg 232	Phe 233	Gly 234	Lys 235	Ala 236	Tyr 237	Asn 238	Leu 239	Arg 240	Ser 241	Val 242	Ala 243
Val 244	Tyr 245	Gly 246	Gly 247	Gly 248	Ser 249	Met 250	Trp 251	Glu 252	Gln 253	Ala 254	Lys 255	Ala 256	Leu 257	Gln 258	Glu 259
Gly 260	Ala 261	Glu 262	Ile 263	Val 264	Val 265	Cys 266	Thr 267	Pro 268	Gly 269	Arg 270	Leu 271	Ile 272	Asp 273	His 274	Val 275
Lys 276	Lys 277	Lys 278	Ala 279	Thr 280	Asn 281	Leu 282	Gln 283	Arg 284	Val 285	Ser 286	Tyr 287	Leu 288	Val 289	Phe 290	Asp 291
Glu 292	Ala 293	Asp 294	Arg 295	Met 296	Phe 297	Asp 298	Met 299	Gly 300	Phe 301	Glu 302	Tyr 303	Gln 304	Val 305	Arg 306	Ser 307
Ile 308	Ala 309	Ser 310	His 311	Val 312	Arg 313	Ile 314	Glu 315	Lys 316	Leu 317	Ala 318	Arg 319	Thr 320	Leu 321	Phe 322	Ala 323
Thr 324	Phe 325	Arg 326	Lys 327	Lys 328	Ile 329	Gln 330	Lys 331	Leu 332	Ala 333	Arg 334	Asp 335	Ile 336	Leu 337	Ile 338	Asp 339
Pro 340	Ile 341	Arg 342	Val 343	Val 344	Gln 345	Gly 346	Asp 347	Ile 348	Gly 349	Glu 350	Ala 351	Asn 352	Glu 353	Asp 354	Val 355

## SEQUENCE LISTING 1657-2022.txt

Thr Gln Ile Val Glu Ile Leu His Ser Gly Pro Ser Lys Trp Asn Trp  
 355 360 365  
 Leu Thr Arg Arg Leu Val Glu Phe Thr Ser Ser Gly Ser Val Leu Leu  
 370 375 380  
 Phe Val Thr Lys Lys Ala Asn Ala Glu Glu Leu Ala Asn Asn Leu Lys  
 385 390 395 400  
 Gln Glu Gly His Asn Leu Gly Leu Leu His Gly Asp Met Asp Gln Ser  
 405 410 415  
 Glu Arg Asn Lys Val Ile Ser Asp Phe Lys Lys Asp Ile Pro Val  
 420 425 430  
 Leu Val Ala Thr Asp Val Ala Ala Arg Gly Leu Asp Ile Pro Ser Ile  
 435 440 445  
 Lys Thr Val Ile Asn Tyr Asp Val Ala Arg Asp Ile Asp Thr His Thr  
 450 455 460  
 His Arg Ile Gly Arg Thr Gly Arg Ala Gly Glu Lys Gly Val Ala Tyr  
 465 470 475 480  
 Thr Leu Leu Thr Pro Lys Asp Ser Asn Phe Ala Gly Asp Leu Val Arg  
 485 490 495  
 Asn Leu Glu Gly Ala Asn Gln His Val Ser Lys Glu Leu Leu Asp Leu  
 500 505 510  
 Ala Met Gln Asn Ala Trp Phe Arg Lys Ser Arg Phe Lys Gly Gly Lys  
 515 520 525  
 Gly Lys Lys Leu Asn Ile Gly Gly Gly Leu Gly Tyr Arg Glu Arg  
 530 535 540  
 Pro Gly Leu Gly Ser Glu Asn Met Asp Arg Gly Asn Asn Asn Val Met  
 545 550 555 560  
 Ser Asn Tyr Glu Ala Tyr Lys Pro Ser Thr Gly Ala Met Gly Asp Arg  
 565 570 575  
 Leu Thr Ala Met Lys Ala Ala Phe Gln Ser Gln Tyr Lys Ser His Phe  
 580 585 590  
 Val Ala Ala Ser Leu Ser Asn Gln Lys Ala Gly Ser Ser Ala Ala Gly  
 595 600 605  
 Ala Ser Gly Trp Thr Ser Ala Gly Ser Leu Asn Ser Val Pro Thr Asn  
 610 615 620  
 Ser Ala Gln Gln Gly His Asn Ser Pro Asp Ser Pro Val Thr Ser Ala  
 625 630 635 640  
 Ala Lys Gly Ile Pro Gly Phe Gly Asn Thr Gly Asn Ile Ser Gly Ala  
 645 650 655  
 Pro Val Thr Tyr Pro Ser Ala Gly Ala Gln Gly Val Asn Asn Thr Ala  
 660 665 670  
 Ser Gly Asn Asn Ser Arg Glu Gly Thr Gly Gly Ser Asn Gly Lys Arg  
 675 680 685  
 Glu Arg Tyr Thr Glu Asn Arg Gly Ser Ser Pro Ser Gln Ser Arg Arg  
 690 695 700  
 Asp Trp Gln Ser Ala  
 705

<210> 178  
 <211> 5178  
 <212> PRT  
 <213> Homo sapiens

<400> 178

Met Gly Leu Pro Leu Ala Arg Leu Ala Ala Val Cys Leu Ala Leu Ser  
 1 5 10 15  
 Leu Ala Gly Gly Ser Glu Leu Gln Thr Glu Gly Arg Thr Arg Tyr His  
 20 25 30  
 Gly Arg Asn Val Cys Ser Thr Trp Gly Asn Phe His Tyr Lys Thr Phe  
 35 40 45  
 Asp Gly Asp Val Phe Arg Phe Pro Gly Leu Cys Asp Tyr Asn Phe Ala  
 50 55 60  
 Ser Asp Cys Arg Gly Ser Tyr Lys Glu Phe Ala Val His Leu Lys Arg  
 65 70 75 80  
 Gly Pro Gly Gln Ala Glu Ala Pro Ala Gly Val Glu Ser Ile Leu Leu  
 85 90 95  
 Thr Ile Lys Asp Asp Thr Ile Tyr Leu Thr Arg His Leu Ala Val Leu

## SEQUENCE LISTING 1657-2022.txt

```

100      105      110
Asn Gly Ala Val Val Ser Thr Pro His Tyr Ser Pro Gly Leu Leu Ile
115      120      125
Glu Lys Ser Asp Ala Tyr Thr Lys Val Tyr Ser Arg Ala Gly Leu Thr
130      135      140
Leu Met Trp Asn Arg Glu Asp Ala Leu Met Leu Glu Leu Asp Thr Lys
145      150      155
Phe Arg Asn His Thr Cys Gly Leu Cys Gly Asp Tyr Asn Gly Leu Gln
165      170      175
Ser Tyr Ser Glu Phe Leu Ser Asp Gly Val Leu Phe Ser Pro Leu Glu
180      185      190
Phe Gly Asn Met Gln Lys Ile Asn Gln Pro Asp Val Val Cys Glu Asp
195      200      205
Pro Glu Glu Glu Val Ala Pro Ala Ser Cys Ser Glu His Arg Ala Glu
210      215      220
Cys Glu Arg Leu Leu Thr Ala Glu Ala Phe Ala Asp Cys Gln Asp Leu
225      230      235
Val Pro Leu Glu Pro Tyr Leu Arg Ala Cys Gln Gln Asp Arg Cys Arg
245      250      255
Cys Pro Gly Gly Asp Thr Cys Val Cys Ser Thr Val Ala Glu Phe Ser
260      265      270
Arg Gln Cys Ser His Ala Gly Gly Arg Pro Gly Asn Trp Arg Thr Ala
275      280      285
Thr Leu Cys Pro Lys Thr Cys Pro Gly Asn Leu Val Tyr Leu Glu Ser
290      295      300
Gly Ser Pro Cys Met Asp Thr Cys Ser His Leu Glu Val Ser Ser Leu
305      310      315
Cys Glu Glu His Arg Met Asp Gly Cys Phe Cys Pro Glu Gly Thr Val
325      330      335
Tyr Asp Asp Ile Gly Asp Ser Gly Cys Val Pro Val Ser Gln Cys His
340      345      350
Cys Arg Leu His Gly His Leu Tyr Thr Pro Gly Gln Glu Ile Thr Asn
355      360      365
Asp Cys Glu Gln Cys Val Cys Asn Ala Gly Arg Trp Val Cys Lys Asp
370      375      380
Leu Pro Cys Pro Gly Thr Cys Ala Leu Glu Gly Ser His Ile Thr
385      390      395
Thr Phe Asp Gly Lys Thr Tyr Thr Phe His Gly Asp Cys Tyr Tyr Val
405      410      415
Leu Ala Lys Gly Asp His Asn Asp Ser Tyr Ala Leu Leu Gly Glu Leu
420      425      430
Ala Pro Cys Gly Ser Thr Asp Lys Gln Thr Cys Leu Lys Thr Val Val
435      440      445
Leu Leu Ala Asp Lys Lys Lys Asn Ala Val Val Phe Lys Ser Asp Gly
450      455      460
Ser Val Leu Leu Asn Gln Leu Gln Val Asn Leu Pro His Val Thr Ala
465      470      475
Ser Phe Ser Val Phe Arg Pro Ser Ser Tyr His Ile Met Val Ser Met
485      490      495
Ala Ile Gly Val Arg Leu Gln Val Gln Leu Ala Pro Val Met Gln Leu
500      505      510
Phe Val Thr Leu Asp Gln Ala Ser Gln Gly Gln Val Gln Gly Leu Cys
515      520      525
Gly Asn Phe Asn Gly Leu Glu Gly Asp Asp Phe Lys Thr Ala Ser Gly
530      535      540
Leu Val Glu Ala Thr Gly Ala Gly Phe Ala Asn Thr Trp Lys Ala Gln
545      550      555
Ser Thr Cys His Asp Lys Leu Asp Trp Leu Asp Asp Pro Cys Ser Leu
565      570      575
Asn Ile Glu Ser Ala Asn Tyr Ala Glu His Trp Cys Ser Leu Lys
580      585      590
Lys Thr Glu Thr Pro Phe Gly Arg Cys His Ser Ala Val Asp Pro Ala
595      600      605
Glu Tyr Tyr Lys Arg Cys Lys Tyr Asp Thr Cys Asn Cys Gln Asn Asn
610      615      620
Glu Asp Cys Leu Cys Ala Ala Leu Ser Ser Tyr Ala Arg Ala Cys Thr
625      630      635      640

```

## SEQUENCE LISTING 1657-2022.txt

Ala Lys Gly Val Met Leu Trp Gly Trp Arg Glu His Val Cys Asn Lys  
 645 650 655  
 Asp Val Gly Ser Cys Pro Asn Ser Gln Val Phe Leu Tyr Asn Leu Thr  
 660 665 670  
 Thr Cys Gln Gln Thr Cys Arg Ser Leu Ser Glu Ala Asp Ser His Cys  
 675 680 685  
 Leu Glu Gly Phe Ala Pro Val Asp Gly Cys Gly Cys Pro Asp His Thr  
 690 695 700  
 Phe Leu Asp Glu Lys Gly Arg Cys Val Pro Leu Ala Lys Cys Ser Cys  
 705 710 715 720  
 Tyr His Arg Gly Leu Tyr Leu Glu Ala Gly Asp Val Val Val Arg Gln  
 725 730 735  
 Glu Glu Arg Cys Val Cys Arg Asp Gly Arg Leu His Cys Arg Gln Ile  
 740 745 750  
 Arg Leu Ile Gly Gln Ser Cys Thr Ala Pro Lys Ile His Met Asp Cys  
 755 760 765  
 Ser Asn Leu Thr Ala Leu Ala Thr Ser Lys Pro Arg Ala Leu Ser Cys  
 770 775 780  
 Gln Thr Leu Ala Ala Gly Tyr Tyr His Thr Glu Cys Val Ser Gly Cys  
 785 790 795 800  
 Val Cys Pro Asp Gly Leu Met Asp Asp Gly Arg Gly Gly Cys Val Val  
 805 810 815  
 Glu Lys Glu Cys Pro Cys Val His Asn Asn Asp Leu Tyr Ser Ser Gly  
 820 825 830  
 Ala Lys Ile Lys Val Asp Cys Asn Thr Cys Thr Cys Lys Arg Gly Arg  
 835 840 845  
 Trp Val Cys Thr Gln Ala Val Cys His Gly Thr Cys Ser Ile Tyr Gly  
 850 855 860  
 Ser Gly His Tyr Ile Thr Phe Asp Gly Lys Tyr Tyr Asp Phe Asp Gly  
 865 870 875 880  
 His Cys Ser Tyr Val Ala Val Gln Asp Tyr Cys Gly Gln Asn Ser Ser  
 885 890 895  
 Leu Gly Ser Phe Ser Ile Ile Thr Glu Asn Val Pro Cys Gly Thr Thr  
 900 905 910  
 Gly Val Thr Cys Ser Lys Ala Ile Lys Ile Phe Met Gly Arg Thr Glu  
 915 920 925  
 Leu Lys Leu Glu Asp Lys His Arg Val Val Ile Gln Arg Asp Glu Gly  
 930 935 940  
 His His Val Ala Tyr Thr Thr Arg Glu Val Gly Gln Tyr Leu Val Val  
 945 950 955 960  
 Glu Ser Ser Thr Gly Ile Ile Val Ile Trp Asp Lys Arg Thr Thr Val  
 965 970 975  
 Phe Ile Lys Leu Ala Pro Ser Tyr Lys Gly Thr Val Cys Gly Leu Cys  
 980 985 990  
 Gly Asn Phe Asp His Arg Ser Asn Asn Asp Phe Thr Thr Arg Asp His  
 995 1000 1005  
 Met Val Val Ser Ser Glu Leu Asp Phe Gly Asn Ser Trp Lys Glu Ala  
 1010 1015 1020  
 Pro Thr Cys Pro Asp Val Ser Thr Asn Pro Glu Pro Cys Ser Leu Asn  
 1025 1030 1035 1040  
 Pro His Arg Arg Ser Trp Ala Glu Lys Gln Cys Ser Ile Leu Lys Ser  
 1045 1050 1055  
 Ser Val Phe Ser Ile Cys His Ser Lys Val Asp Pro Lys Pro Phe Tyr  
 1060 1065 1070  
 Glu Ala Cys Val His Asp Ser Cys Ser Cys Asp Thr Gly Gly Asp Cys  
 1075 1080 1085  
 Glu Cys Phe Cys Ser Ala Val Ala Ser Tyr Ala Gln Glu Cys Thr Lys  
 1090 1095 1100  
 Glu Gly Ala Cys Val Phe Trp Arg Thr Pro Asp Leu Cys Pro Ile Phe  
 1105 1110 1115 1120  
 Cys Asp Tyr Tyr Asn Pro Pro His Glu Cys Glu Trp His Tyr Glu Pro  
 1125 1130 1135  
 Cys Gly Asn Arg Ser Phe Glu Thr Cys Arg Thr Ile Asn Gly Ile His  
 1140 1145 1150  
 Ser Asn Ile Ser Val Ser Tyr Leu Glu Gly Cys Tyr Pro Arg Cys Pro  
 1155 1160 1165  
 Lys Asp Arg Pro Ile Tyr Glu Glu Asp Leu Lys Lys Cys Val Thr Ala

## SEQUENCE LISTING 1657-2022.txt

1170  
 Asp Lys Cys Gly Cys Tyr Val Glu Asp Thr His Tyr Pro Pro Gly Ala  
 1185  
 Ser Val Pro Thr Glu Thr Cys Lys Ser Cys Val Cys Thr Asn Ser  
 1205  
 Ser Gln Val Val Cys Arg Pro Glu Glu Gly Lys Ile Leu Asn Gln Thr  
 1220  
 Gln Asp Gly Ala Phe Cys Tyr Trp Glu Ile Cys Gly Pro Asn Gly Thr  
 1235  
 Val Glu Lys His Phe Asn Ile Cys Ser Ile Thr Thr Arg Pro Ser Thr  
 1250  
 Leu Thr Thr Phe Thr Thr Ile Thr Leu Pro Thr Thr Pro Thr Ser Phe  
 1265  
 Thr Thr Thr Thr Thr Thr Thr Thr Pro Thr Ser Ser Thr Val Leu Ser  
 1285  
 Thr Thr Pro Lys Leu Cys Cys Leu Trp Ser Asp Trp Ile Asn Glu Asp  
 1300  
 His Pro Ser Ser Gly Ser Asp Asp Gly Asp Arg Glu Pro Phe Asp Gly  
 1315  
 Val Cys Gly Ala Pro Glu Asp Ile Glu Cys Arg Ser Val Lys Asp Pro  
 1330  
 His Leu Ser Leu Glu Gln His Gly Gln Lys Val Gln Cys Asp Val Ser  
 1345  
 Val Gly Phe Ile Cys Lys Asn Glu Asp Gln Phe Gly Asn Gly Pro Phe  
 1365  
 Gly Leu Cys Tyr Asp Tyr Lys Ile Arg Val Asn Cys Cys Trp Pro Met  
 1380  
 Asp Lys Cys Ile Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro  
 1395  
 Pro Pro Thr Thr Thr Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro  
 1410  
 Pro Thr Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
 1425  
 Pro Ile Thr Thr Thr Thr Thr Thr Pro Leu Pro Thr Thr Thr Pro Ser Pro  
 1445  
 Pro Ile Ser Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
 1460  
 Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr  
 1475  
 Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Met  
 1490  
 Thr Thr Pro Ile Thr Pro Pro Ala Ser Thr Thr Thr Leu Pro Pro Thr  
 1505  
 Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr  
 1525  
 Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser  
 1540  
 Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr  
 1555  
 Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr  
 1570  
 Thr Pro Ser Pro Pro Thr Ile Thr Thr Thr Pro Pro Pro Thr Thr  
 1585  
 Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr  
 1605  
 Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser Thr  
 1620  
 Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Thr  
 1635  
 Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr  
 1650  
 Pro Ser Pro Pro Ile Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr  
 1665  
 Pro Ser Ser Pro Ile Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met  
 1685  
 Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Ser Pro Ile Thr Thr Thr  
 1700  
 1705  
 1710



## SEQUENCE LISTING 1657-2022.txt

Thr Thr Pro Ser Ser Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Met  
1715 1720 1725  
Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met  
1730 1735 1740  
Thr Thr Leu Pro Pro Thr Thr Thr Ser Ser Pro Leu Thr Thr Thr Pro  
1745 1750 1755 1760  
Leu Pro Pro Ser Ile Thr Pro Pro Thr Phe Ser Pro Phe Ser Thr Thr  
1765 1770 1775  
Thr Pro Thr Thr Pro Cys Val Pro Leu Cys Asn Trp Thr Gly Trp Leu  
1780 1785 1790  
Asp Ser Gly Lys Pro Asn Phe His Lys Pro Gly Gly Asp Thr Glu Leu  
1795 1800 1805  
Ile Gly Asp Val Cys Gly Pro Gly Trp Ala Ala Asn Ile Ser Cys Arg  
1810 1815 1820  
Ala Thr Met Tyr Pro Asp Val Pro Ile Gly Gln Leu Gly Gln Thr Val  
1825 1830 1835 1840  
Val Cys Asp Val Ser Val Gly Leu Ile Cys Lys Asn Glu Asp Gln Lys  
1845 1850 1855  
Pro Gly Gly Val Ile Pro Met Ala Phe Cys Leu Asn Tyr Glu Ile Asn  
1860 1865 1870  
Val Gln Cys Cys Glu Cys Val Thr Gln Pro Thr Thr Met Thr Thr Thr  
1875 1880 1885  
Thr Thr Glu Asn Pro Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr  
1890 1895 1900  
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## SEQUENCE LISTING 1657-2022.txt

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Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
2340 2345 2350  
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Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
2370 2375 2380  
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2385 2390 2395 2400  
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2770 2775 2780

## SEQUENCE LISTING 1657-2022.txt

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Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
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Gln Thr Pro Thr Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
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3285 3290 3295  
Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
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## SEQUENCE LISTING 1657-2022.txt

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Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
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3525  
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3540  
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3555  
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## SEQUENCE LISTING 1657-2022.txt

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 Leu Pro Pro Ala Ile Glu Met Thr Ser Thr Ala Pro Pro Ser Thr Pro  
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 Thr Ala Pro Thr Thr Thr Ser Gly Gly His Thr Leu Ser Pro Pro Pro  
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 4275 4280 4285  
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 4290 4295 4300  
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 4305 4310 4315 4320  
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## SEQUENCE LISTING 1657-2022.txt

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    4450                                      4455                                      4460  
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    4565                                      4570                                      4575  
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    4580                                      4585                                      4590  
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    4595                                      4600                                      4605  
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    4675                                      4680                                      4685  
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    4690                                      4695                                      4700  
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## SEQUENCE LISTING 1657-2022.txt

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 Leu Met Glu Arg Ile Gln Leu Pro Trp Asp Ser Val Gly Arg Leu Glu  
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 145 150 155 160  
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 165 170 175  
 Ala Asn Trp Met Glu Ser Ser Ser Trp Asp Gly Arg Tyr Ala Met Val  
 180 185 190  
 Val Cys Gly Asp Ile Ala Val Tyr Pro Ser Gly Asn Ala Arg Pro Thr  
 195 200 205  
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 Page 173

## SEQUENCE LISTING 1657-2022.txt

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 Phe Tyr Lys Pro Asn Leu Ala Ser Glu Tyr Pro Ile Val Asp Gly Lys  
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 Tyr Arg Lys Lys Ile Gln Asn Gln Trp Lys Gln Ala Gly Ser Asp Arg  
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 Pro Phe Thr Leu Asp Asp Leu Gln Tyr Met Ile Phe His Thr Pro Phe  
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 Cys Lys Met Val Gln Lys Ser Leu Ala Arg Leu Met Phe Asn Asp Phe  
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 Leu Ser Ala Ser Ser Asp Thr Gln Thr Ser Leu Tyr Lys Gly Leu Glu  
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 Ala Phe Gly Gly Leu Lys Leu Glu Asp Thr Tyr Thr Asn Lys Asp Leu  
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 Lys Ala Ser Leu Tyr Leu Ser Thr His Asn Gly Asn Met Tyr Thr Ser  
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 Ser Leu Tyr Gly Cys Leu Ala Ser Leu Leu Ser His His Ser Ala Gln  
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 Glu Gly Ile Val Val Ala Ile Asp Pro Asn Val Pro Glu Asp Glu Thr  
 10  
 Leu Ile Gln Gln Ile Lys Asp Met Val Thr Gln Ala Ser Leu Tyr Leu  
 15  
 Phe Glu Ala Thr Gly Lys Arg Phe Tyr Phe Lys Asn Val Ala Ile Leu  
 20  
 Ile Pro Glu Thr Trp Lys Thr Lys Ala Asp Tyr Val Arg Pro Lys Leu  
 25  
 Glu Thr Tyr Lys Asn Ala Asp Val Leu Val Ala Glu Ser Thr Pro Pro  
 30  
 Gly Asn Asp Glu Pro Tyr Thr Glu Gln Met Gly Asn Cys Gly Glu Lys  
 35  
 Gly Glu Arg Ile His Leu Thr Pro Asp Phe Ile Ala Gly Lys Lys Leu  
 40  
 Ala Glu Tyr Gly Pro Gln Gly Lys Ala Phe Val His Glu Trp Ala His  
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 Leu Arg Trp Gly Val Phe Asp Glu Tyr Asn Asn Asp Glu Lys Phe Tyr  
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 165  
 170  
 175



## SEQUENCE LISTING 1657-2022.txt

Leu Ser Asn Gly Arg Ile Gln Ala Val Arg Cys Ser Ala Gly Ile Thr  
 Gly Thr Asn Val Val Lys Lys Cys Gln Gly Gly Ser Cys Tyr Thr Lys  
 Arg Cys Thr Phe Asn Lys Val Thr Gly Leu Tyr Glu Lys Gly Cys Glu  
 Phe Val Leu Gln Ser Arg Gln Thr Glu Lys Ala Ser Ile Met Phe Ala  
 Gln His Val Asp Ser Ile Val Glu Phe Cys Thr Glu Gln Asn His Asn  
 Lys Glu Ala Pro Asn Lys Gln Asn Gln Lys Cys Asn Leu Arg Ser Thr  
 Trp Glu Val Ile Arg Asp Ser Glu Asp Phe Lys Lys Thr Thr Pro Met  
 Thr Thr Gln Pro Pro Asn Pro Thr Phe Ser Leu Leu Gln Ile Gly Gln  
 Arg Ile Val Cys Leu Val Leu Asp Lys Ser Gly Ser Met Ala Thr Gly  
 Asn Arg Leu Asn Arg Leu Asn Gln Ala Gly Gln Leu Phe Leu Leu Gln  
 Thr Val Glu Leu Gly Ser Trp Val Gly Met Val Thr Phe Asp Ser Ala  
 Ala His Val Gln Ser Glu Leu Ile Gln Ile Asn Ser Gly Ser Asp Arg  
 Asp Thr Leu Ala Lys Arg Leu Pro Ala Ala Ala Ser Gly Gly Thr Ser  
 Ile Cys Ser Gly Leu Arg Ser Ala Phe Thr Val Ile Arg Lys Lys Tyr  
 Pro Thr Asp Gly Ser Glu Ile Val Leu Leu Thr Asp Gly Glu Asp Asn  
 Thr Ile Ser Gly Cys Phe Asn Glu Val Lys Gln Ser Gly Ala Ile Ile  
 His Thr Val Ala Leu Gly Pro Ser Ala Ala Gln Glu Leu Glu Glu Leu  
 Ser Lys Met Thr Gly Gly Leu Gln Thr Tyr Ala Ser Asp Gln Val Gln  
 Asn Asn Gly Leu Ile Asp Ala Phe Gly Ala Leu Ser Ser Gly Asn Gly  
 Ala Val Ser Gln Arg Ser Ile Gln Leu Glu Ser Lys Gly Leu Thr Leu  
 Gln Asn Ser Gln Trp Met Asn Gly Thr Val Ile Val Asp Ser Thr Val  
 Gly Lys Asp Thr Leu Phe Leu Ile Thr Trp Thr Thr Gln Pro Pro Gln  
 Ile Leu Leu Trp Asp Pro Ser Gly Gln Lys Gln Gly Phe Val Val  
 Asp Lys Asn Thr Lys Met Ala Tyr Leu Gln Ile Pro Gly Ile Ala Lys  
 Val Gly Thr Trp Lys Tyr Ser Leu Gln Ala Ser Ser Gln Thr Leu Thr  
 Leu Thr Val Thr Ser Arg Ala Ser Asn Ala Thr Leu Pro Pro Ile Thr  
 Val Thr Ser Lys Thr Asn Lys Asp Thr Ser Lys Phe Pro Ser Pro Leu  
 Val Val Tyr Ala Asn Ile Arg Gln Gly Ala Ser Pro Ile Leu Arg Ala  
 Ser Val Thr Ala Leu Ile Glu Ser Val Asn Gly Lys Thr Val Thr Leu  
 Glu Leu Leu Asp Asn Gly Ala Gly Ala Asp Ala Thr Lys Asp Asp Gly  
 Val Tyr Ser Arg Tyr Phe Thr Thr Tyr Asp Thr Asn Gly Arg Tyr Ser  
 Val Lys Val Arg Ala Leu Gly Gly Val Asn Ala Ala Arg Arg Arg Val  
 Ile Pro Gln Gln Ser Gly Ala Leu Tyr Ile Pro Gly Trp Ile Glu Asn  
 Asp Glu Ile Gln Trp Asn Pro Pro Arg Pro Glu Ile Asn Lys Asp Asp

## SEQUENCE LISTING 1657-2022.txt

```

705          710          715          720
Val Gln His Lys Gln Val Cys Phe Ser Arg Thr Ser Ser Gly Gly Ser
725          730          735
Phe Val Ala Ser Asp Val Pro Asn Ala Pro Ile Pro Asp Leu Phe Pro
740          745          750
Pro Gly Gln Ile Thr Asp Leu Lys Ala Glu Ile His Gly Gly Ser Leu
755          760          765
Ile Asn Leu Thr Trp Thr Ala Pro Gly Asp Asp Tyr Asp His Gly Thr
770          775          780
Ala His Lys Tyr Ile Ile Arg Ile Ser Thr Ser Ile Leu Asp Leu Arg
785          790          795          800
Asp Lys Phe Asn Glu Ser Leu Gln Val Asn Thr Thr Ala Leu Ile Pro
805          810          815
Lys Glu Ala Asn Ser Glu Glu Val Phe Leu Phe Lys Pro Glu Asn Ile
820          825          830
Thr Phe Glu Asn Gly Thr Asp Leu Phe Ile Ala Ile Gln Ala Val Asp
835          840          845
Lys Val Asp Leu Lys Ser Glu Ile Ser Asn Ile Ala Arg Val Ser Leu
850          855          860
Phe Ile Pro Pro Gln Thr Pro Pro Glu Thr Pro Ser Pro Asp Glu Thr
865          870          875          880
Ser Ala Pro Cys Pro Asn Ile His Ile Asn Ser Thr Ile Pro Gly Ile
885          890          895
His Ile Leu Lys Ile Met Trp Lys Trp Ile Gly Glu Leu Gln Leu Ser
900          905          910
Ile Ala

```

<210> 181  
 <211> 61  
 <212> PRT  
 <213> Homo sapiens

```

<400> 181
Met Asp Pro Asn Cys Ser Cys Ala Ala Gly Val Ser Cys Thr Cys Ala
1      5      10      15
Gly Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
20      25      30
Cys Cys Ser Cys Cys Pro Val Gly Cys Ser Lys Cys Ala Gln Gly Cys
35      40      45
Val Cys Lys Gly Ala Ser Glu Lys Cys Ser Cys Cys Asp
50      55      60

```

<210> 182  
 <211> 260  
 <212> PRT  
 <213> Homo sapiens

```

<400> 182
Met Ser His His Trp Gly Tyr Gly Lys His Asn Gly Pro Glu His Trp
1      5      10      15
His Lys Asp Phe Pro Ile Ala Lys Gly Glu Arg Gln Ser Pro Val Asp
20      25      30
Ile Asp Thr His Thr Ala Lys Tyr Asp Pro Ser Leu Lys Pro Leu Ser
35      40      45
Val Ser Tyr Asp Gln Ala Thr Ser Leu Arg Ile Leu Asn Asn Gly His
50      55      60
Ala Phe Asn Val Glu Phe Asp Asp Ser Gln Asp Lys Ala Val Leu Lys
65      70      75      80
Gly Gly Pro Leu Asp Gly Thr Tyr Arg Leu Ile Gln Phe His Phe His
85      90      95
Trp Gly Ser Leu Asp Gly Gln Gly Ser Glu His Thr Val Asp Lys Lys
100      105      110
Lys Tyr Ala Ala Glu Leu His Leu Val His Trp Asn Thr Lys Tyr Gly
115      120      125

```

## SEQUENCE LISTING 1657-2022.txt

```

Asp Phe Gly Lys Ala Val Gln Gln Pro Asp Gly Leu Ala Val Leu Gly
130 135 140
Ile Phe Leu Lys Val Gly Ser Ala Lys Pro Gly Leu Gln Lys Val Val
145 150 155 160
Asp Val Leu Asp Ser Ile Lys Thr Lys Gly Lys Ser Ala Asp Phe Thr
165 170 175
Asn Phe Asp Pro Arg Gly Leu Leu Pro Glu Ser Leu Asp Tyr Trp Thr
180 185 190
Tyr Pro Gly Ser Leu Thr Thr Pro Pro Leu Leu Glu Cys Val Thr Trp
195 200 205
Ile Val Leu Lys Glu Pro Ile Ser Val Ser Ser Glu Gln Val Leu Lys
210 215 220
Phe Arg Lys Leu Asn Phe Asn Gly Glu Gly Glu Pro Glu Glu Leu Met
225 230 235 240
Val Asp Asn Trp Arg Pro Ala Gln Pro Leu Lys Asn Arg Gln Ile Lys
245 250 255
Ala Ser Phe Lys
260

```

```

<210> 183
<211> 61
<212> PRT
<213> Homo sapiens

```

```

<400> 183
Met Asp Pro Asn Cys Ser Cys Glu Ala Gly Gly Ser Cys Ala Cys Ala
1 5 10 15
Gly Ser Cys Lys Cys Lys Lys Cys Lys Cys Thr Ser Cys Lys Lys Ser
20 25 30
Cys Cys Ser Cys Cys Pro Leu Gly Cys Ala Lys Cys Ala Gln Gly Cys
35 40 45
Ile Cys Lys Gly Ala Ser Glu Lys Cys Ser Cys Cys Ala
50 55 60

```

```

<210> 184
<211> 61
<212> PRT
<213> Homo sapiens

```

```

<400> 184
Met Asp Pro Asn Cys Ser Cys Ala Ala Gly Val Ser Cys Thr Cys Ala
1 5 10 15
Ser Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
20 25 30
Cys Cys Ser Cys Cys Pro Val Gly Cys Ala Lys Cys Ala Gln Gly Cys
35 40 45
Ile Cys Lys Gly Ala Ser Glu Lys Cys Ser Cys Cys Ala
50 55 60

```

```

<210> 185
<211> 167
<212> PRT
<213> Homo sapiens

```

```

<400> 185
Met Leu Thr Val Ala Leu Leu Ala Leu Leu Cys Ala Ser Ala Ser Gly
1 5 10 15
Asn Ala Ile Gln Ala Arg Ser Ser Tyr Ser Gly Glu Tyr Gly Ser
20 25 30
Gly Gly Gly Lys Arg Phe Ser His Ser Gly Asn Gln Leu Asp Gly Pro
35 40 45
Ile Thr Ala Leu Arg Val Arg Val Asn Thr Tyr Tyr Ile Val Gly Leu
50 55 60
Gln Val Arg Tyr Gly Lys Val Trp Ser Asp Tyr Val Gly Gly Arg Asn
Page 177

```

## SEQUENCE LISTING 1657-2022.txt

```

65      70      75      80
Gly Asp Leu Glu Glu Ile Phe Leu His Pro Gly Glu Ser Val Ile Gln
85
Val Ser Gly Lys Tyr Lys Trp Tyr Leu Lys Lys Leu Val Phe Val Thr
100
Asp Lys Gly Arg Tyr Leu Ser Phe Gly Lys Asp Ser Gly Thr Ser Phe
115
Asn Ala Val Pro Leu His Pro Asn Thr Val Leu Arg Phe Ile Ser Gly
130
Arg Ser Gly Ser Leu Ile Asp Ala Ile Gly Leu His Trp Asp Val Tyr
145
Pro Thr Ser Cys Ser Arg Cys
165

```

&lt;210&gt; 186

&lt;211&gt; 61

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 186

```

Met Asp Pro Asn Cys Ser Cys Ser Pro Val Gly Ser Cys Ala Cys Ala
1      5      10      15
Gly Ser Cys Lys Cys Lys Glu Cys Lys Cys Thr Ser Cys Lys Lys Ser
20      25      30
Cys Cys Ser Cys Cys Pro Val Gly Cys Ala Lys Cys Ala Gln Gly Cys
35      40      45
Ile Cys Lys Gly Thr Ser Asp Lys Cys Ser Cys Cys Ala
50      55      60

```